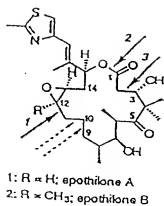
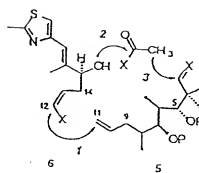


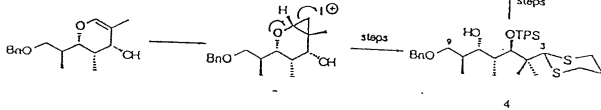
(A)



steps



steps



(B)

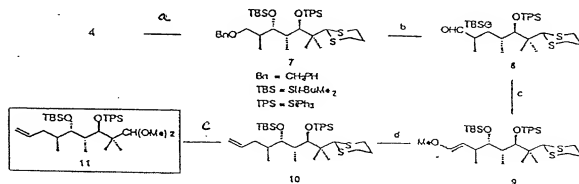


Figure 1

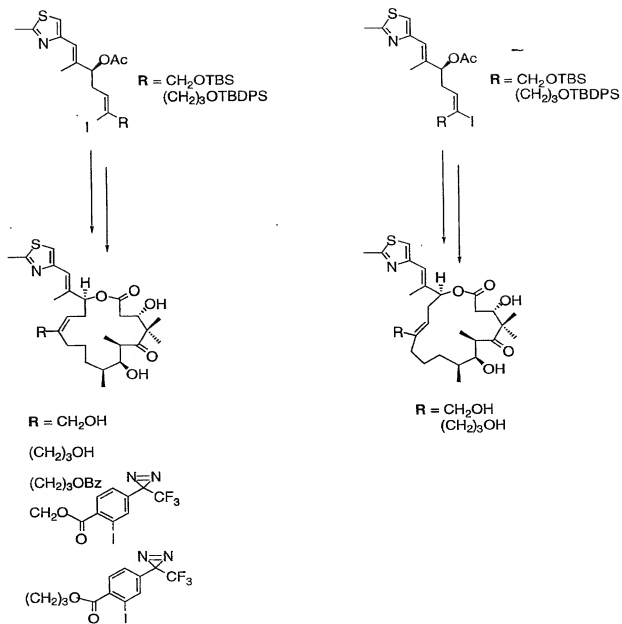


Figure 2

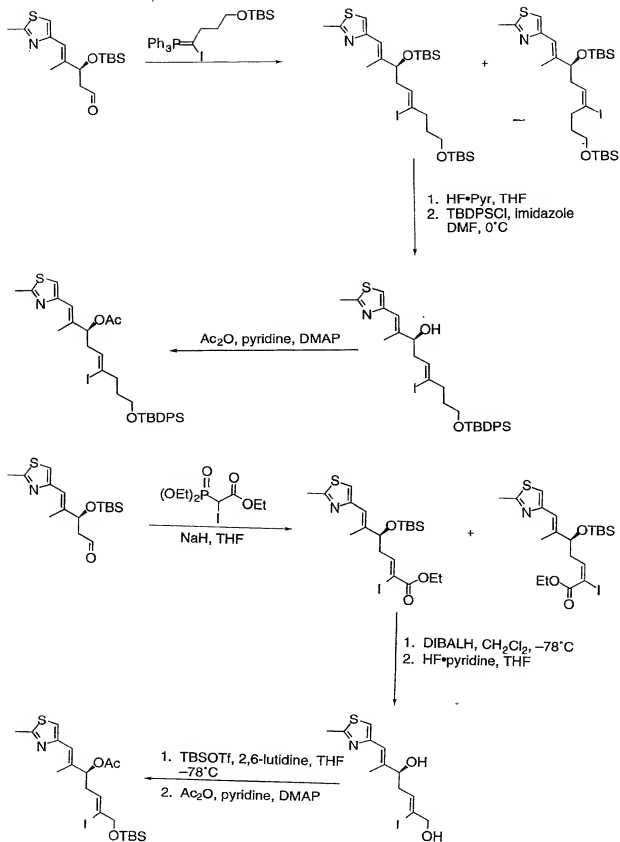


Figure 3(A)

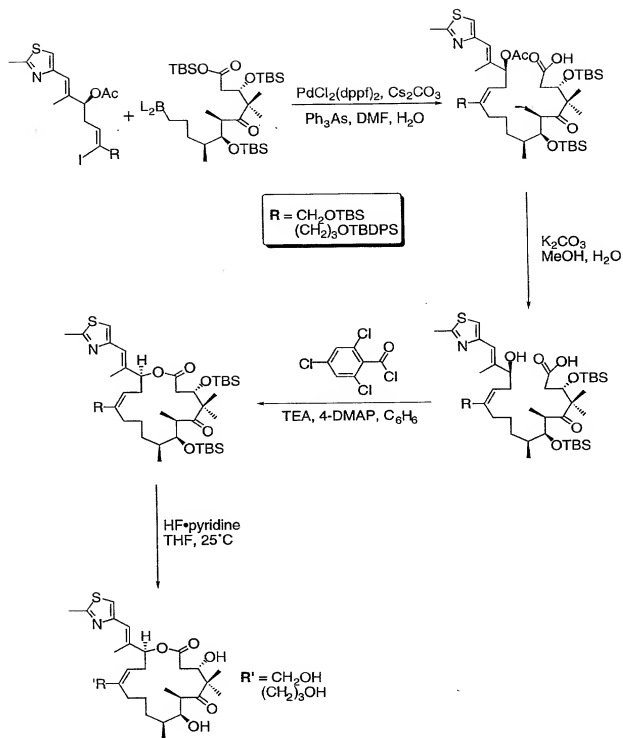


Fig. 3(B)

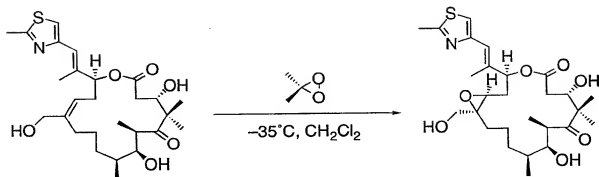
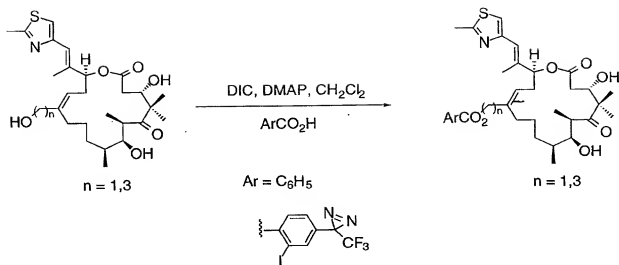


Fig. 3(C)

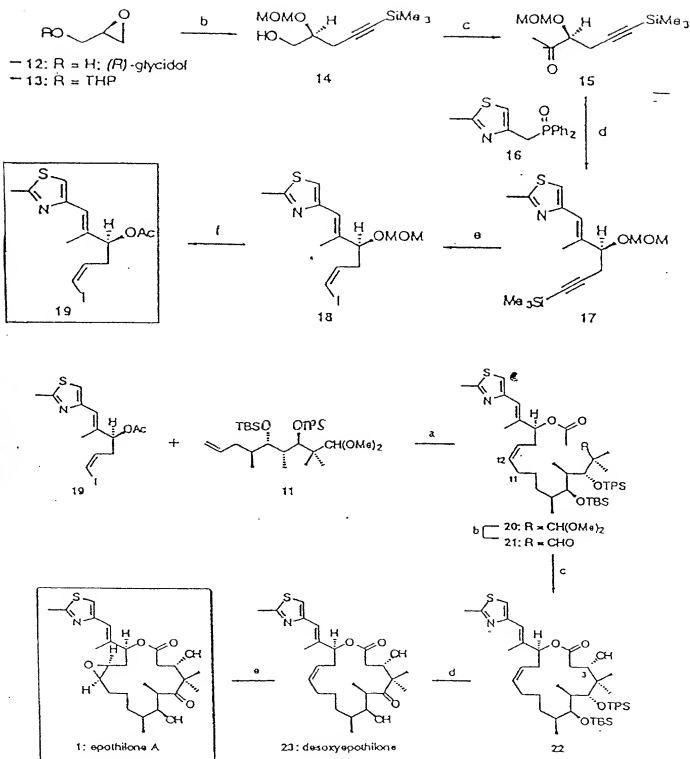


Figure 4

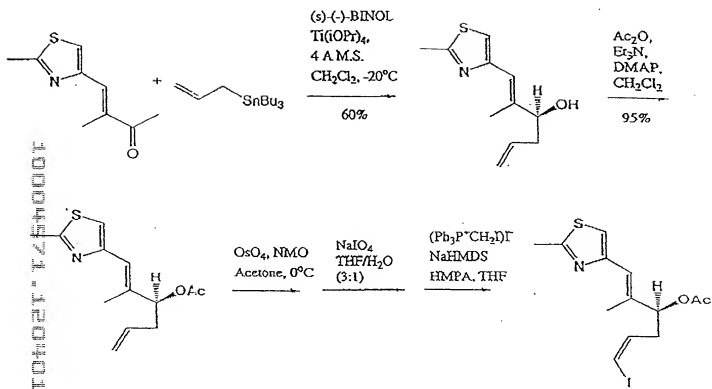
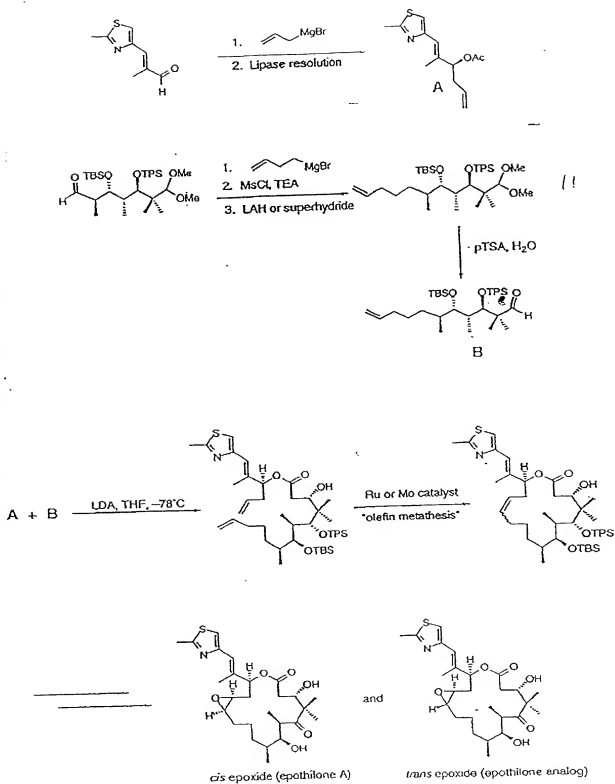
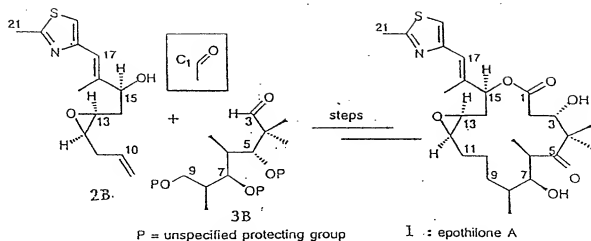


Figure 5



* 17 steps from known starting materials vs. 27 steps for aldol macrocyclization

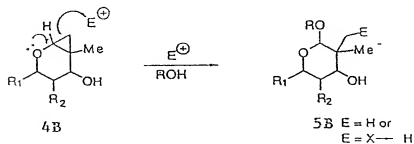
Figure 6



P = unspecified protecting group

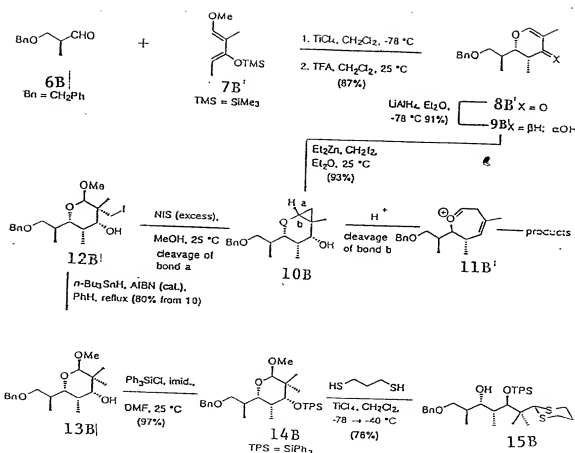
1 \therefore epothilone A

Convergent strategy for a total synthesis of epothilone A (1).



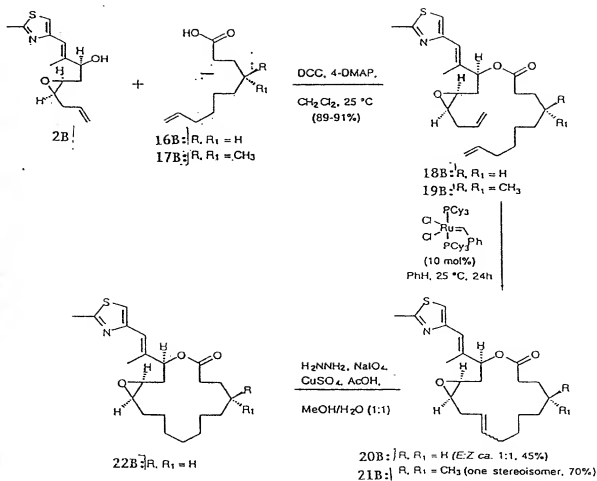
The glycol cyclopropane solvolysis strategy for the introduction of geminal methyl groups.

Figure 7



Enantioselective synthesis of compound **15B**

Figure 8



Construction of epothilone model systems 20^B, 21^B, and 22^B by ring-closing olefin metathesis

Figure 9

100004574.120404

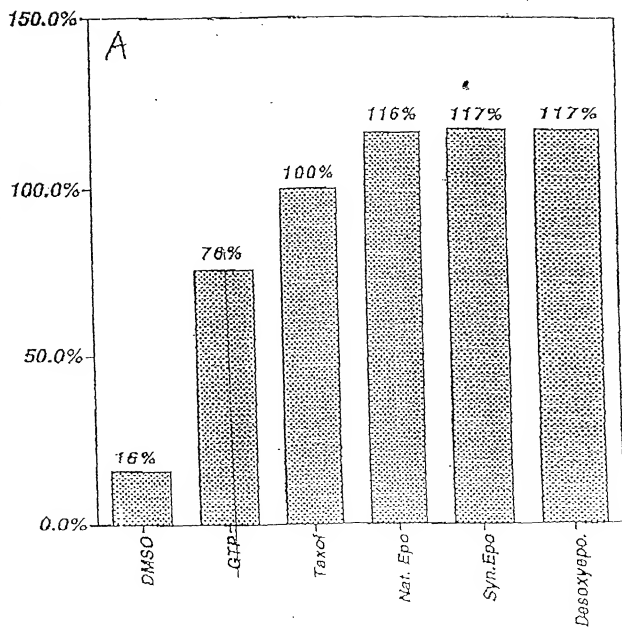


Figure 10

10004571.120401

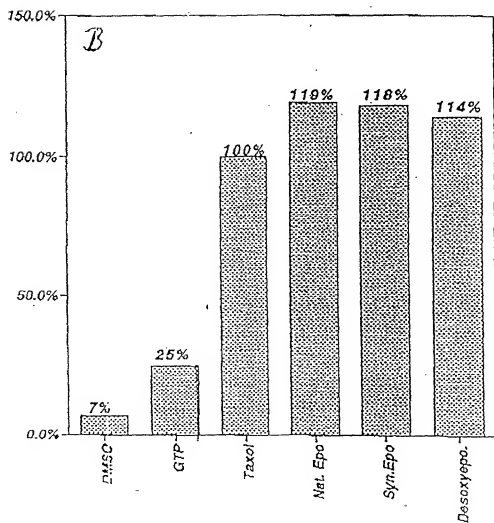
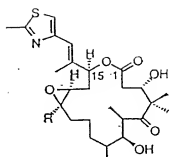
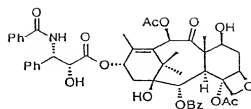


Figure 11



(A)

R = H; epothilone A
R = CH₃; epothilone B



(B)

1A:taxol™

Figure 12

5A + 6A $\xrightarrow{\text{diene-aldehyde cyclocondensation}}$ 7A

7A $\xrightarrow{\text{4 steps}}$ 8A

8A $\xrightarrow{\text{oxidative cleavage}}$ 8A

9A: $R_1, R_2 = \text{H or alkyl}$

Figure 13

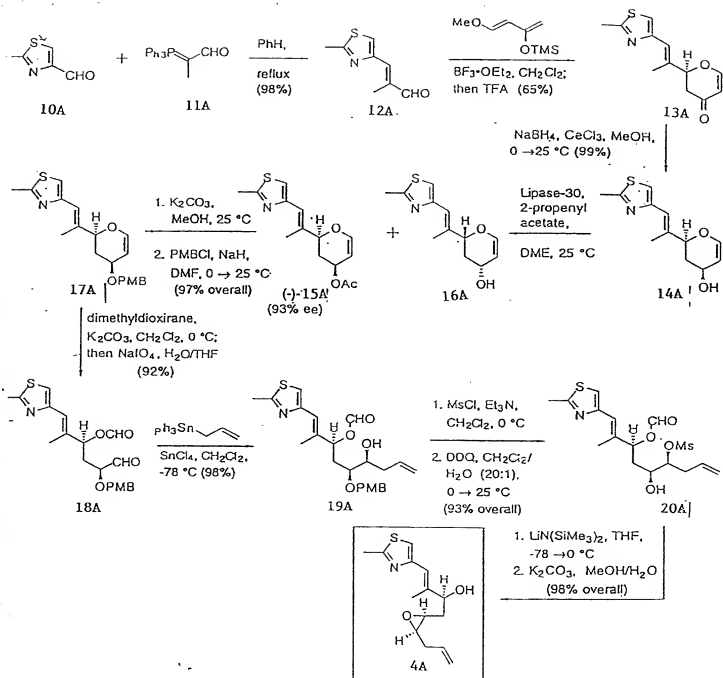


Figure 14

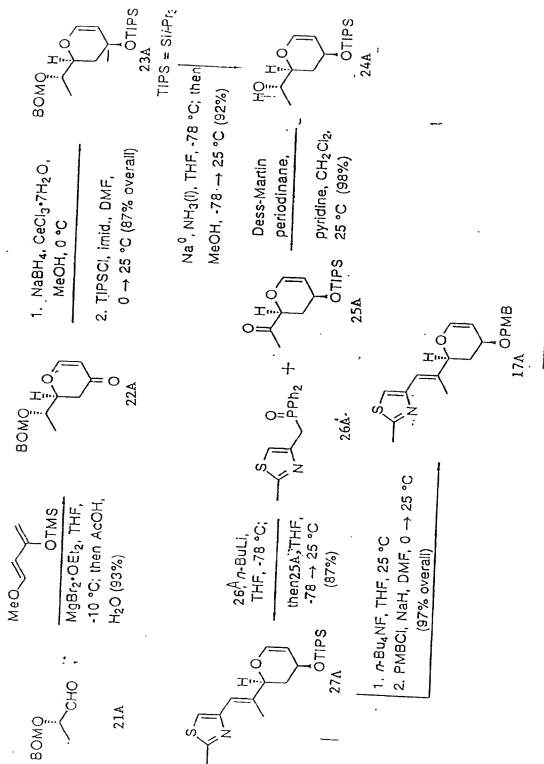


Figure 15

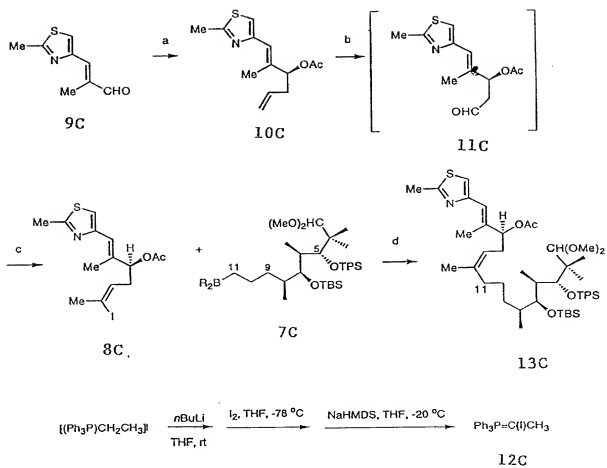


Figure 16

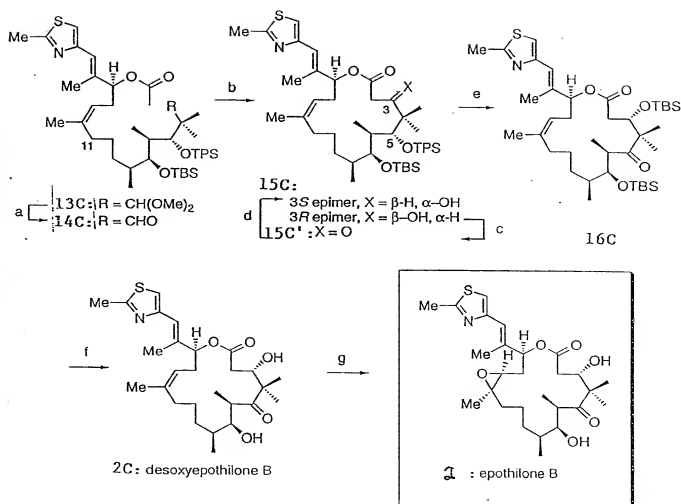


Figure 17

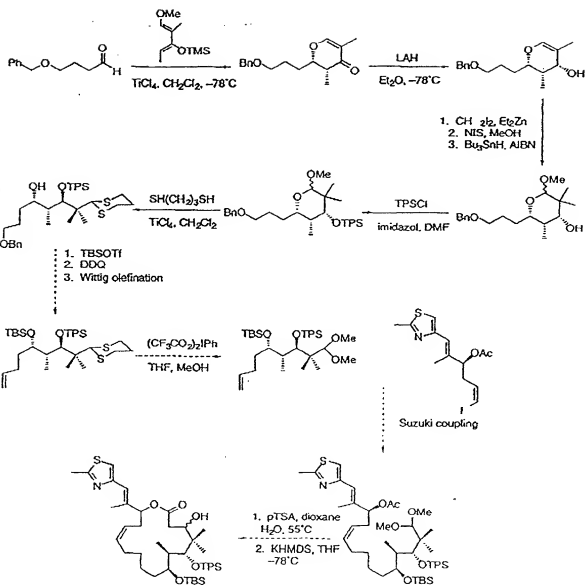


Figure 18

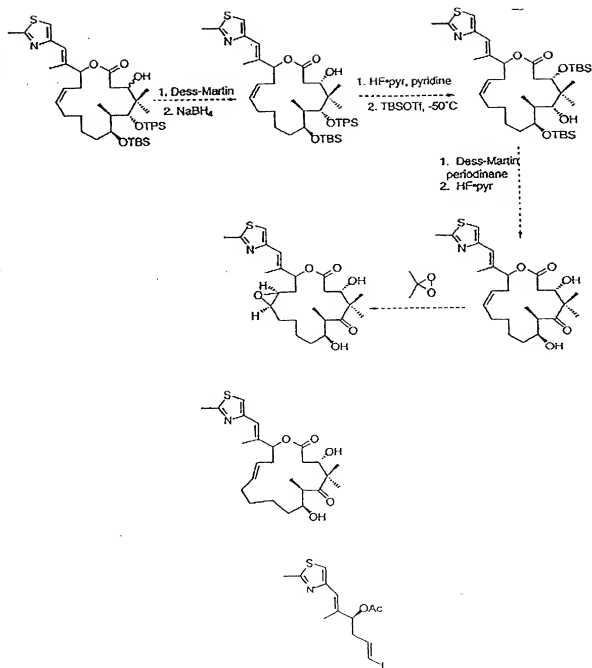


Figure 19

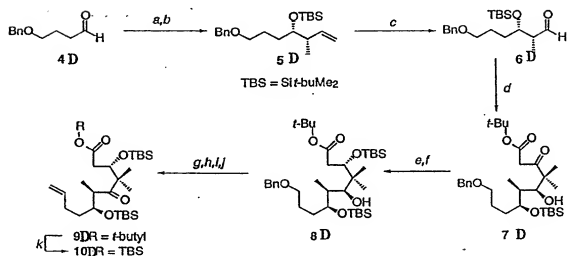
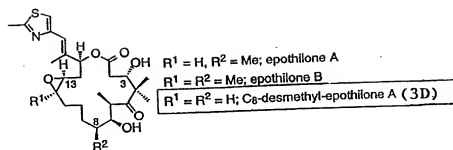


FIGURE 20

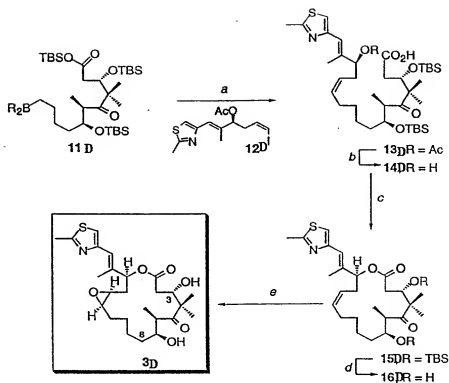


FIGURE 21

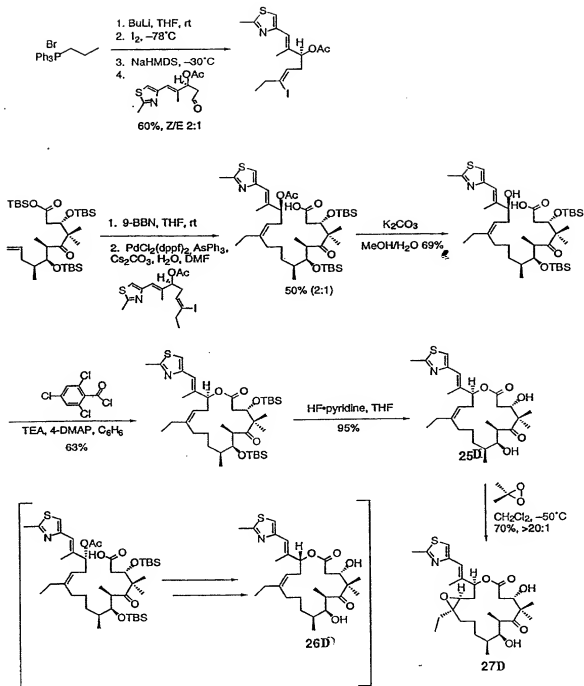


FIGURE 22

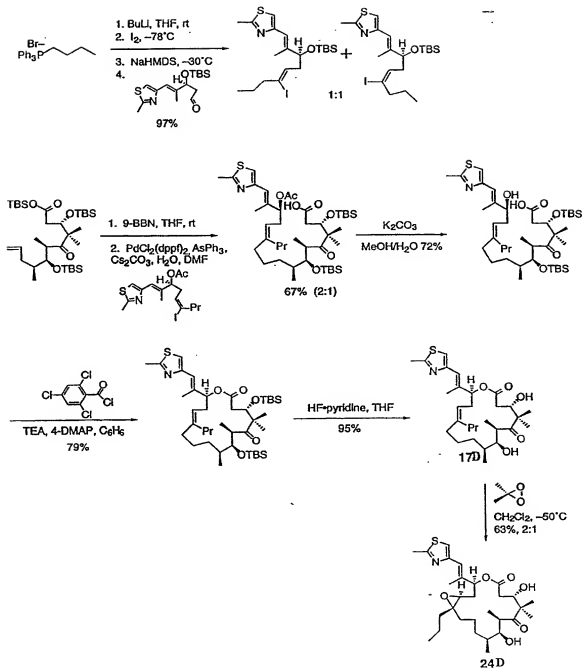


FIGURE 23

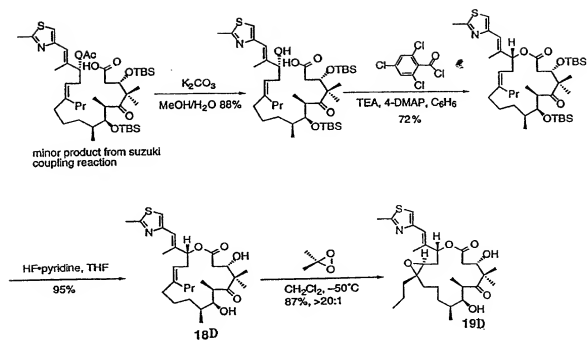


FIGURE 24

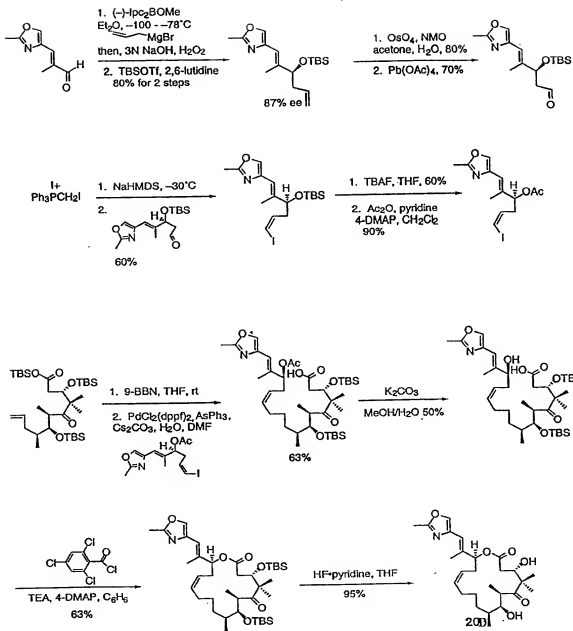


FIGURE 25

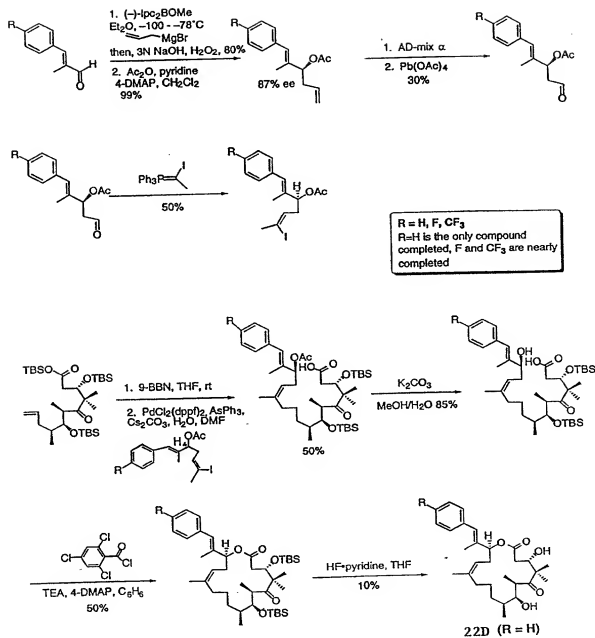


FIGURE 26

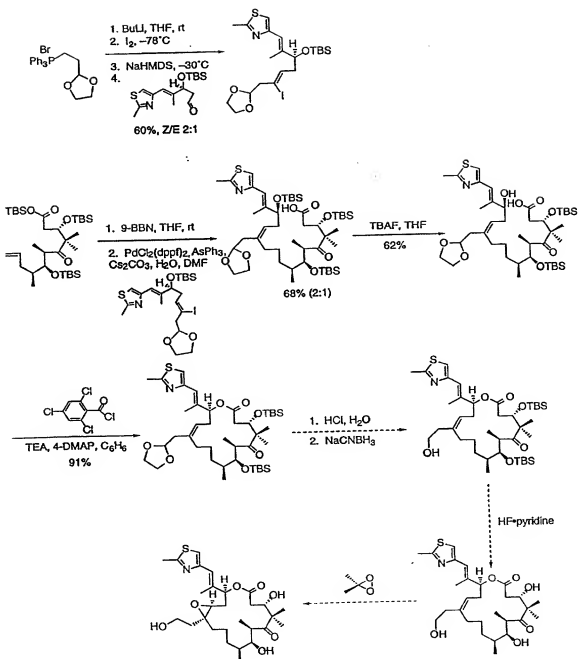


FIGURE 27

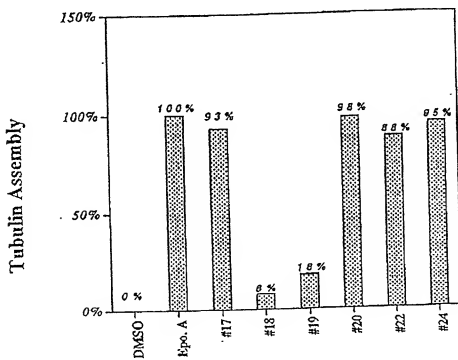
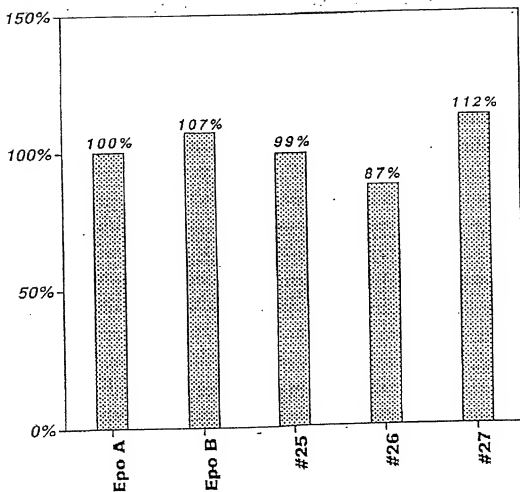


FIGURE 28

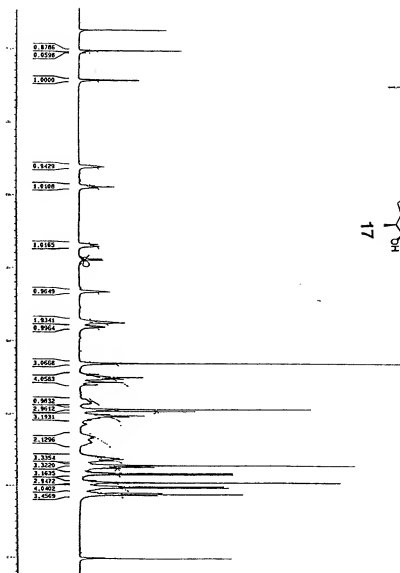
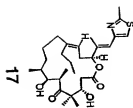


FIGURE 29

2004-2005

2004

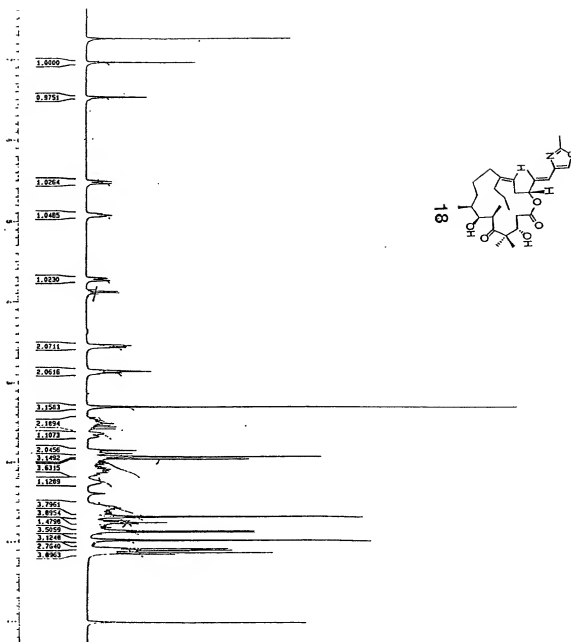


FIGURE 30

10004571.120401

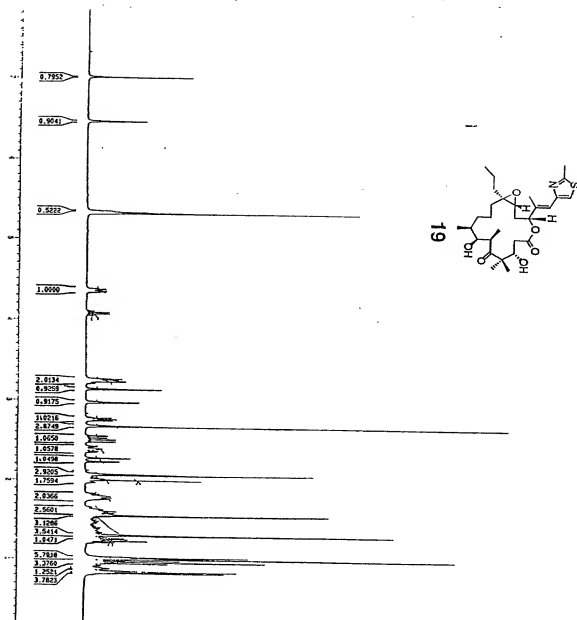


FIGURE 31

10004571.120401

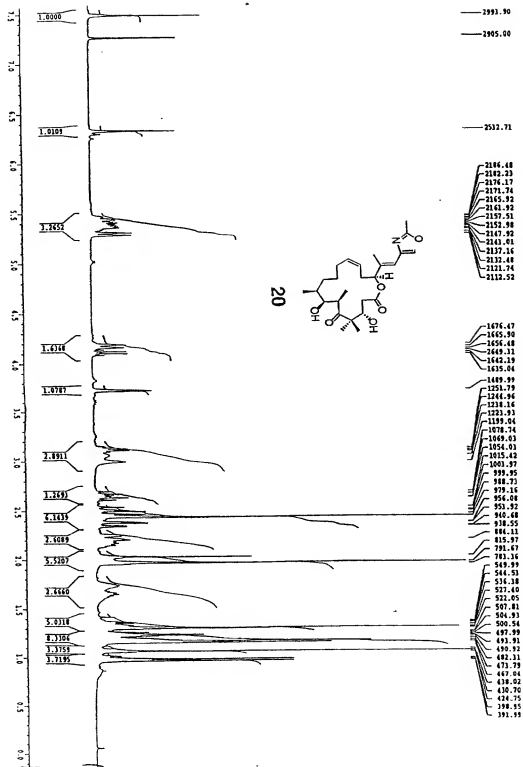


FIGURE 32

10004571.120401

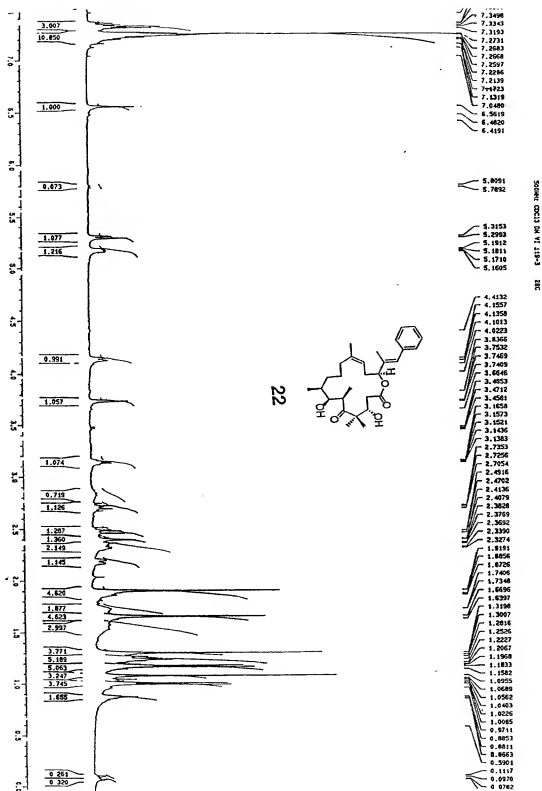


FIGURE 33

055-11-35-1

2051.51
2063.15
2061.81
2056.96
2051.43
2046.76

1724.19
1712.17

1452.79
1450.68
1438.54
1395.66
1374.64
1372.31

1365.71
1365.53
1365.77
1361.62
1378.31
1371.41

1056.46
1056.27
995.28
984.36
980.89
969.83

923.79
921.15
914.91
908.60
906.67

849.40
807.59
799.54
792.79
777.56

761.34
692.48
578.57
578.06
525.16

519.44
514.25
479.66
472.61
469.75

412.19
403.19
401.27
400.88
379.44

374.24
370.77
369.89

25

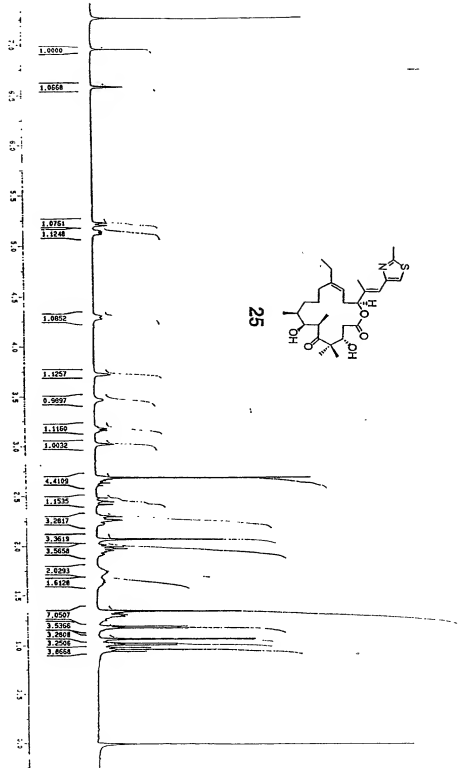
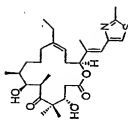


FIGURE 35

10004571.120401

OS5-11-138-11



FIGURE 37

2043-3001

COMBINATION INDEX

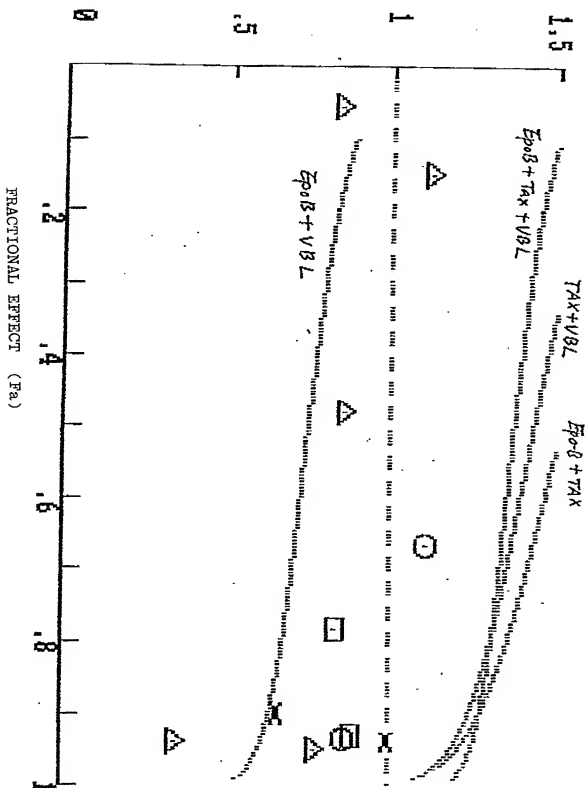
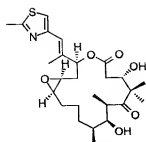
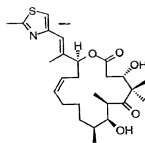


Figure 38

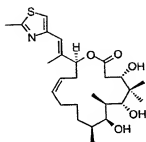
J0004571.120401



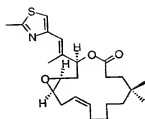
epothilone A
(0.0027)
[0.020]



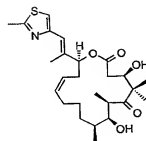
desoxyepothilone A
1
(0.022)
[0.012]



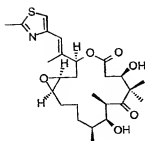
2
(14.23)
[6.28]



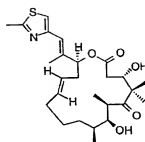
3
(271.1)
[22.4]



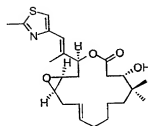
4
(2.12)
[43.0]



5
(>20)
[35.2]

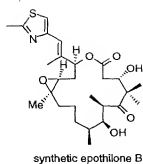


6
(0.052)
[0.035]



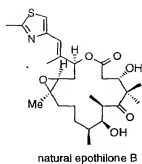
7
(7.36)
[9.82]

Fig. 39



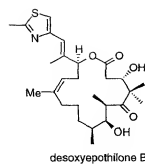
synthetic epothilone B

8
(0.00044)
[0.0026]



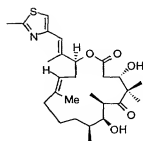
natural epothilone B

9
(0.00017)
[0.0012]

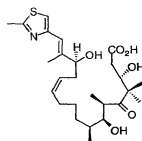


desoxyepothilone B

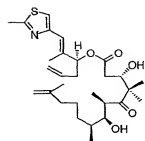
10
(0.0095)
[0.017]



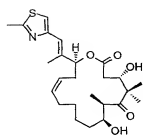
11
(0.090)
[0.262]



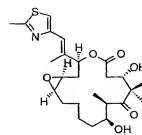
12
(0.79)
[>5]



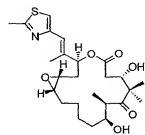
13
(11.53)
[5.63]



14
(5.42)
[5.75]

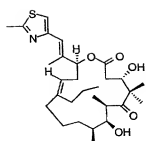


15
(0.96)
[5.95]

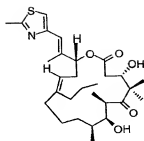


16
(7.47)
[16.48]

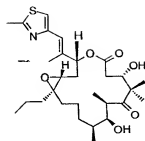
Fig. 40



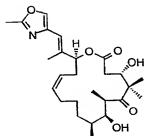
17
(0.090)
[0.254]



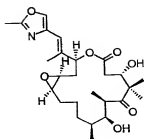
18
(1158)
[>720]



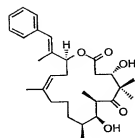
19
(0.96)
[>1.0]



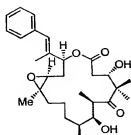
20
(0.030)
[0.049]



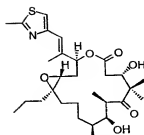
21



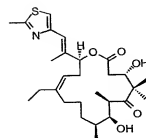
22
(0.098)
[0.146]



23

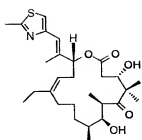


24
(0.0043)
[0.0321]

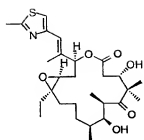


25
(0.021)
[0.0771]

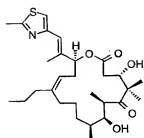
Fig. 41



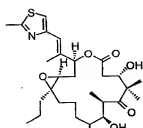
26
(0.055)
[0.197]



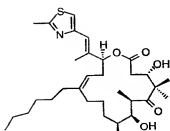
27
(0.0010)
[0.0072]



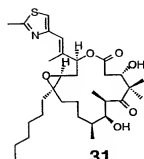
28
(0.039)
[0.067]



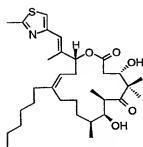
29
(0.0038)
[0.0064]



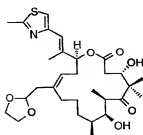
30
(0.044)
[0.108]



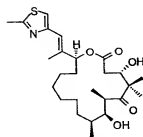
31
(0.027)
[0.049]



32
(0.063)
[0.380]

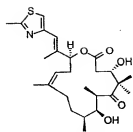


33
(0.0031)
[0.0093]

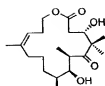


34
(0.143)
[0.276]

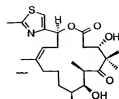
Fig. 42(A)



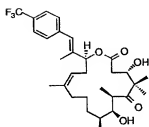
35
(>10)
[8.95]



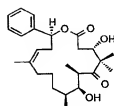
36
(234.5)
[>10]



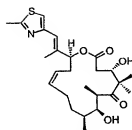
37
(3.25)
[1.20]



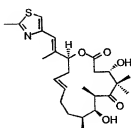
38
(0.254)
[>5.0]



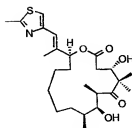
39
(1.80)
[>5.0]



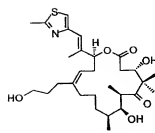
40
(36.9)
[47.3]



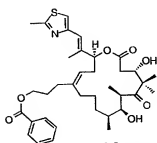
41
(60.1)
[59.2]



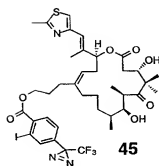
42
(7.41)
[12.9]



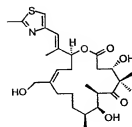
43
(0.0095)
[0.167]



44 (0.250)
[0.905]



45



46 (0.049)
[>1.0]

Fig. 42(B)

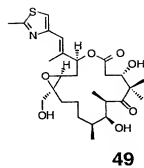
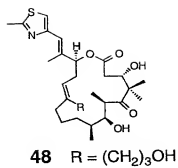
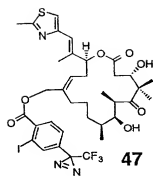


Fig. 42(C)

Fig. 43(A)

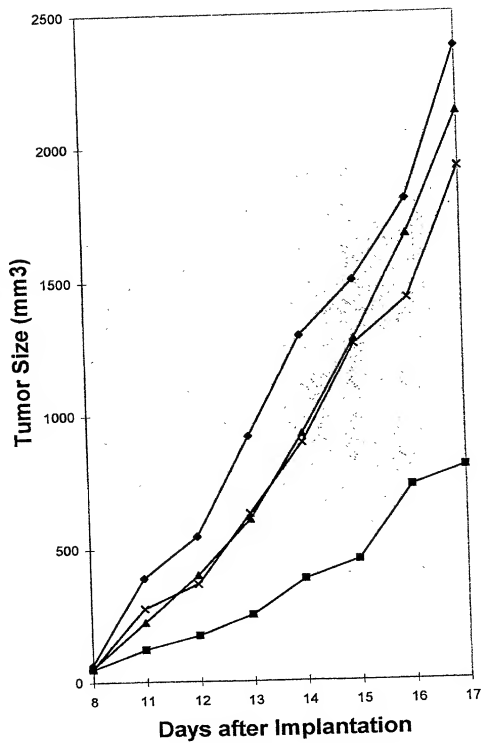
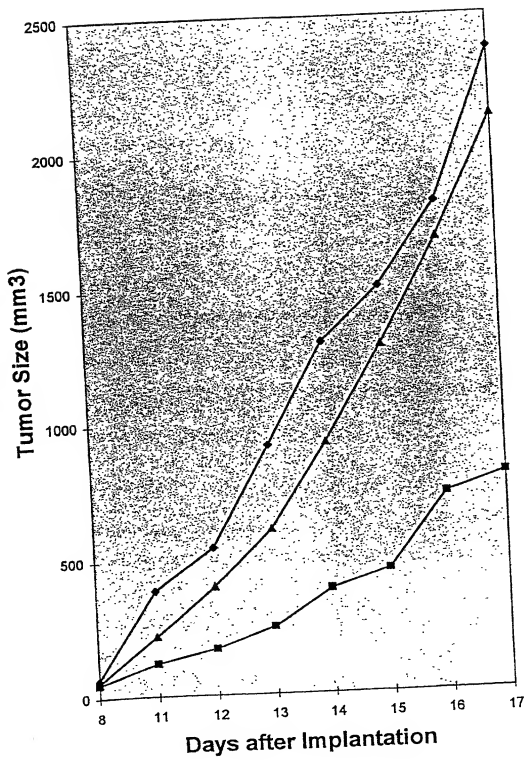


Fig. 43(B)



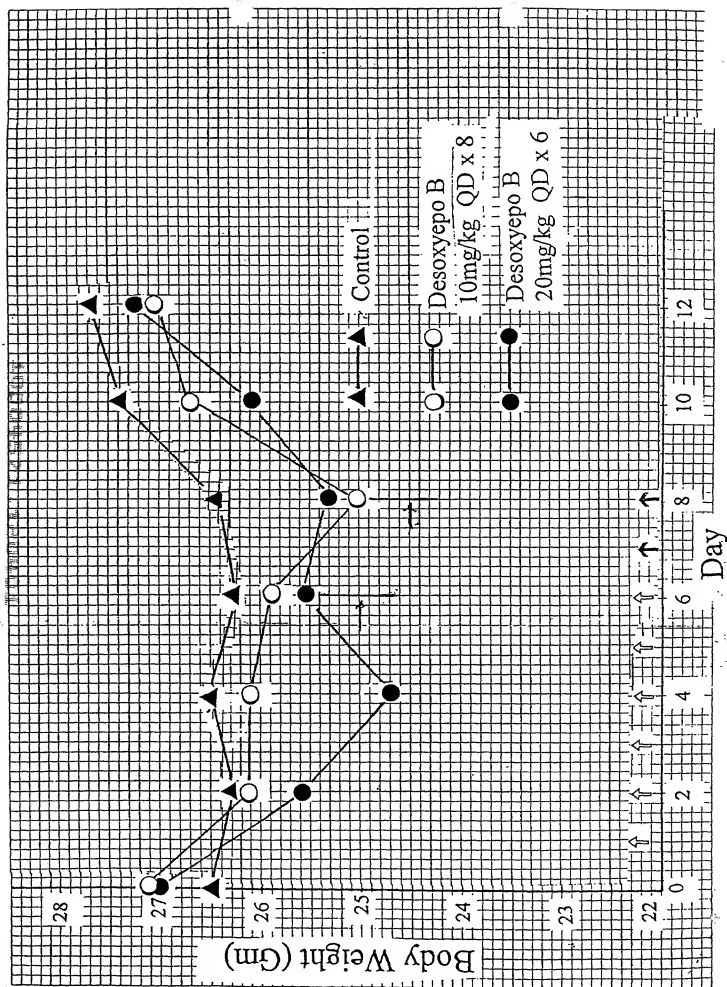


Fig. 44(A)

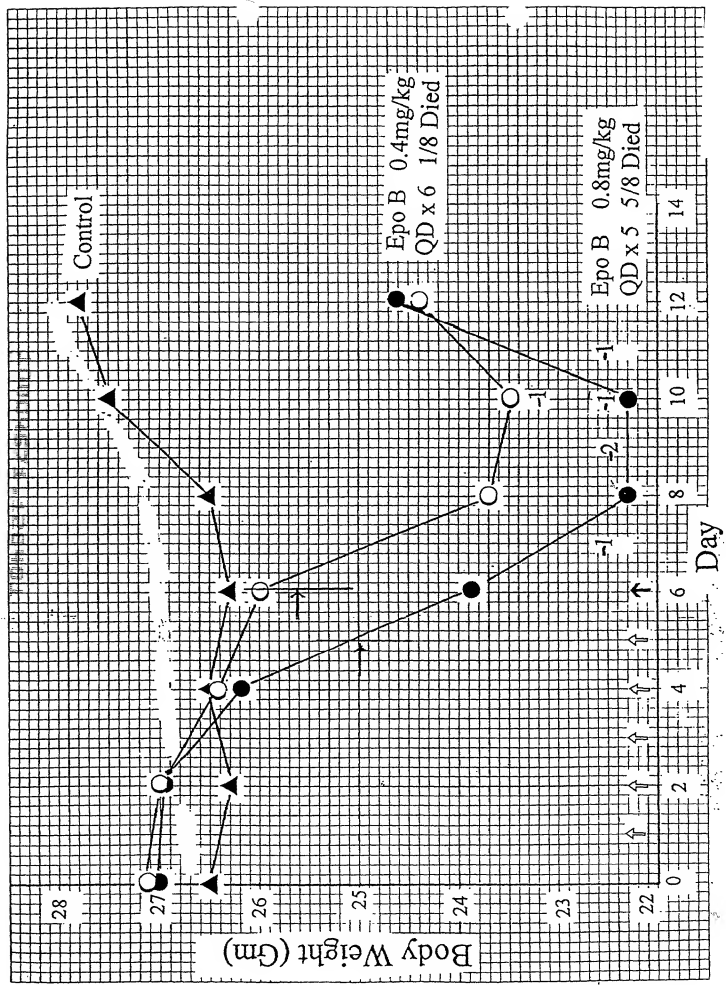


Fig. 44(B)

Fig. 45(A)

101027-125403.01
Tumor size (mm)

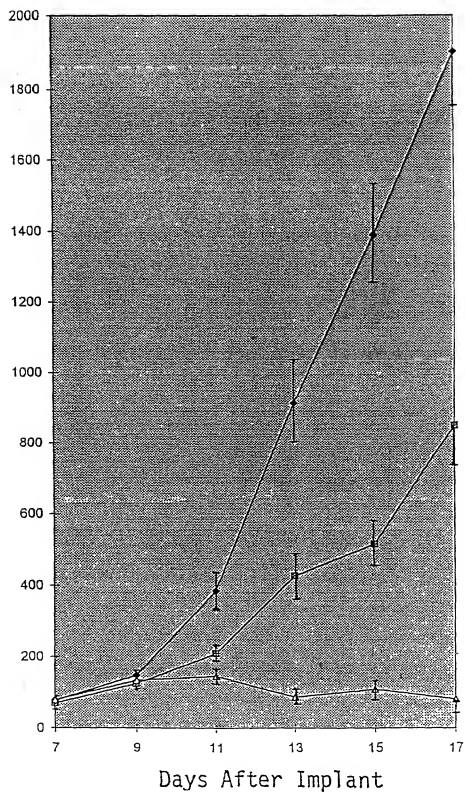
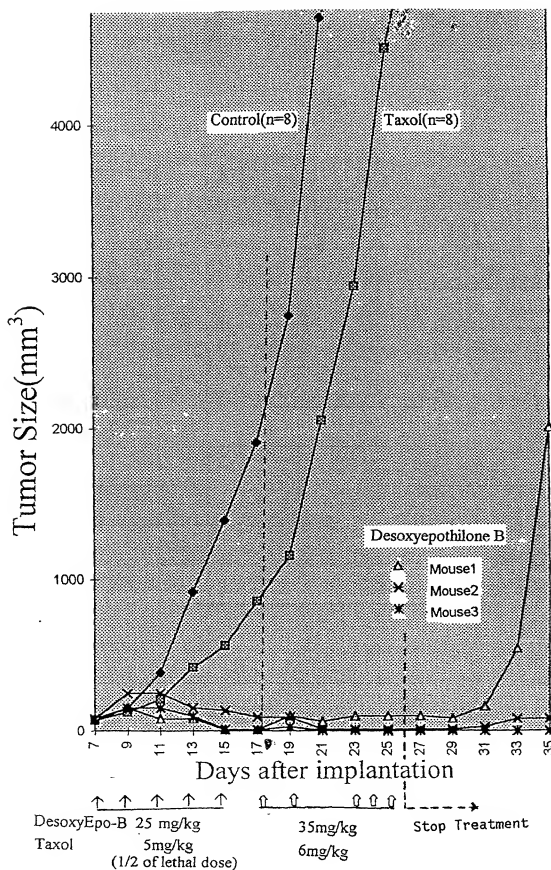


Fig. 45(B)



10004571.1204007

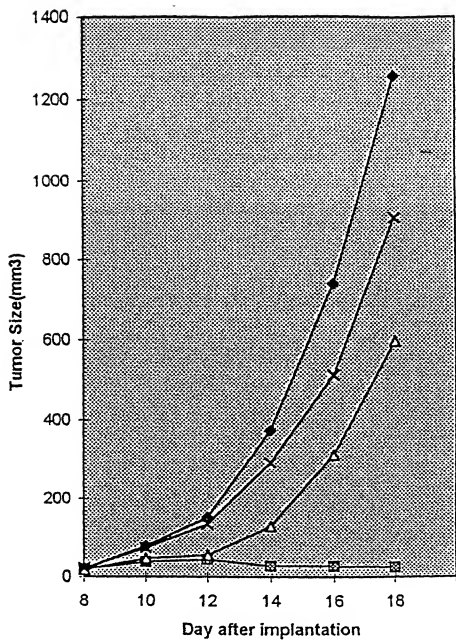
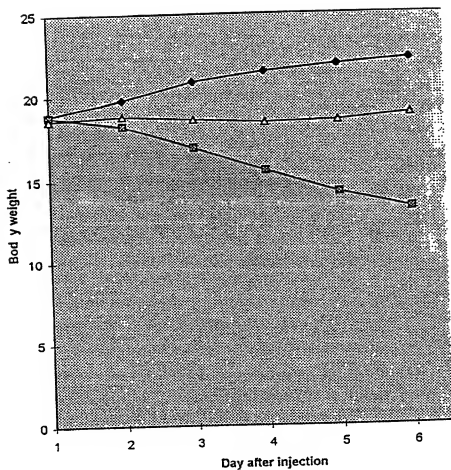
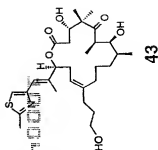


Fig. 46

Fig. 47





43

400 MHz, CDCl₃, rt.

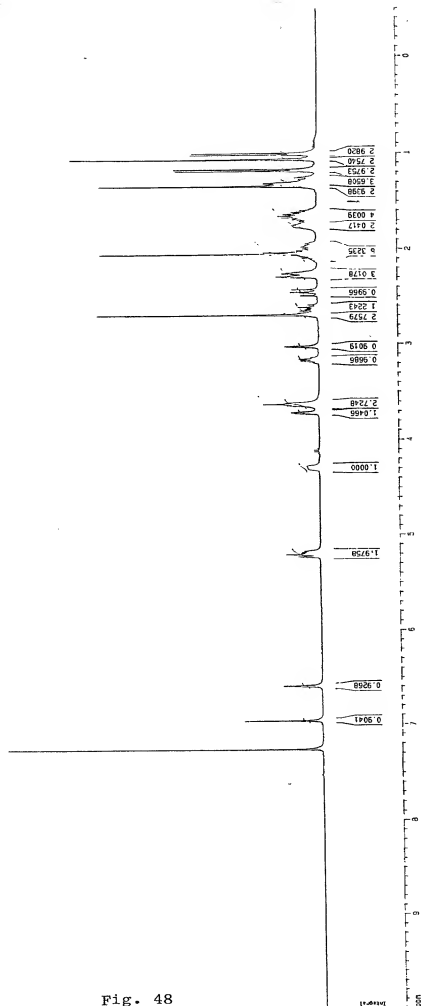


Fig. 48

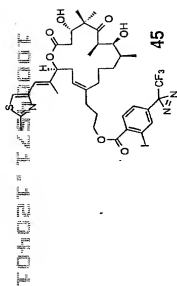
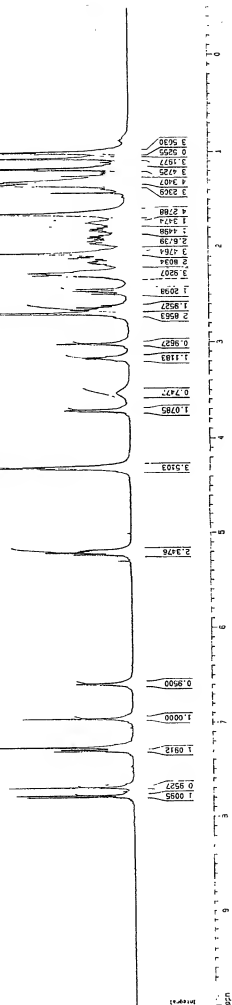
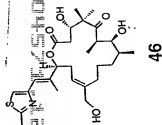


Fig. 49

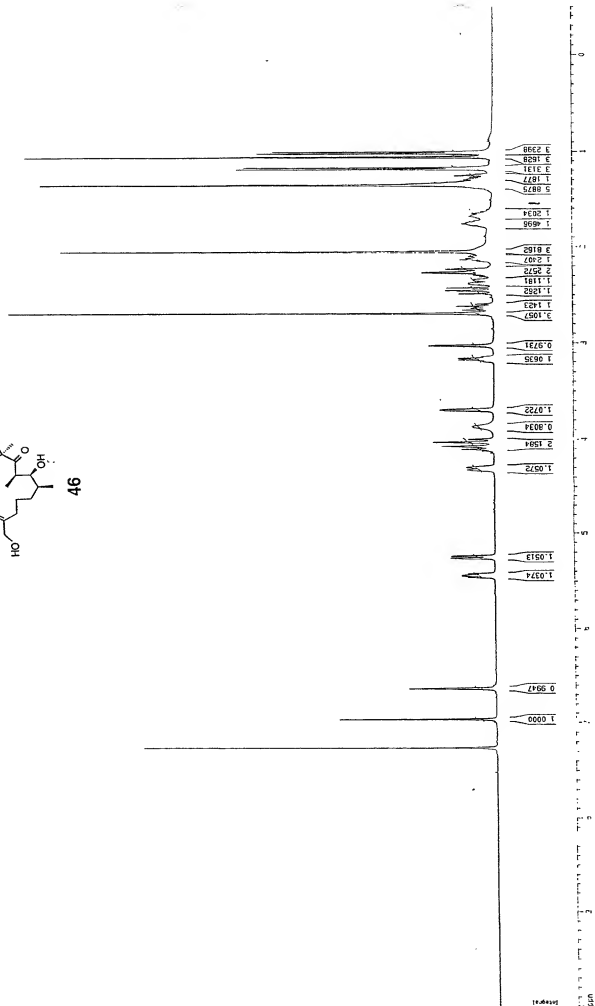


100% Satisfaction

400 MHz, $cdCl_3$, rt.



46



500 MHz. CDCl₃, rt, crude alcohol mosher

III AC264
11/12/97

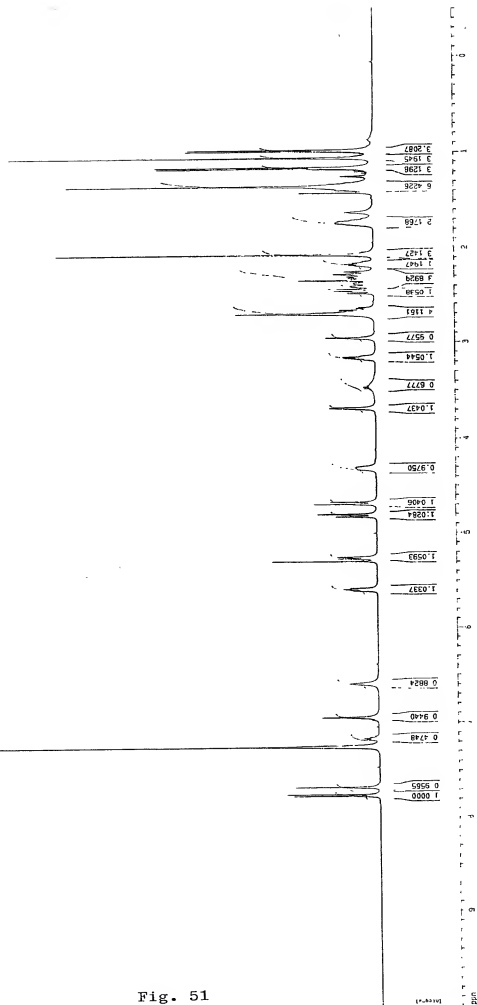
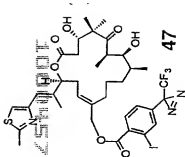
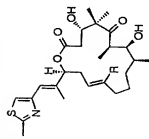


Fig. 51

10004571 12540001



162.4, 11
153.1, 26
143.8, 42
137.9, 27
122.0, 22
105.0, 14
102.9, 28
100.0, 23
95.0, 97
90.0, 94
87.0, 63
83.0, 15
81.0, 13
79.0, 12
77.0, 11
75.0, 10
73.0, 9
71.0, 8
69.0, 7
67.0, 6
65.0, 5
63.0, 4
61.0, 3
59.0, 2
57.0, 1

162.4, 11
153.1, 26
143.8, 42
137.9, 27
122.0, 22
105.0, 14
102.9, 28
100.0, 23
95.0, 97
90.0, 94
87.0, 63
83.0, 15
81.0, 13
79.0, 12
77.0, 11
75.0, 10
73.0, 9
71.0, 8
69.0, 7
67.0, 6
65.0, 5
63.0, 4
61.0, 3
59.0, 2
57.0, 1

162

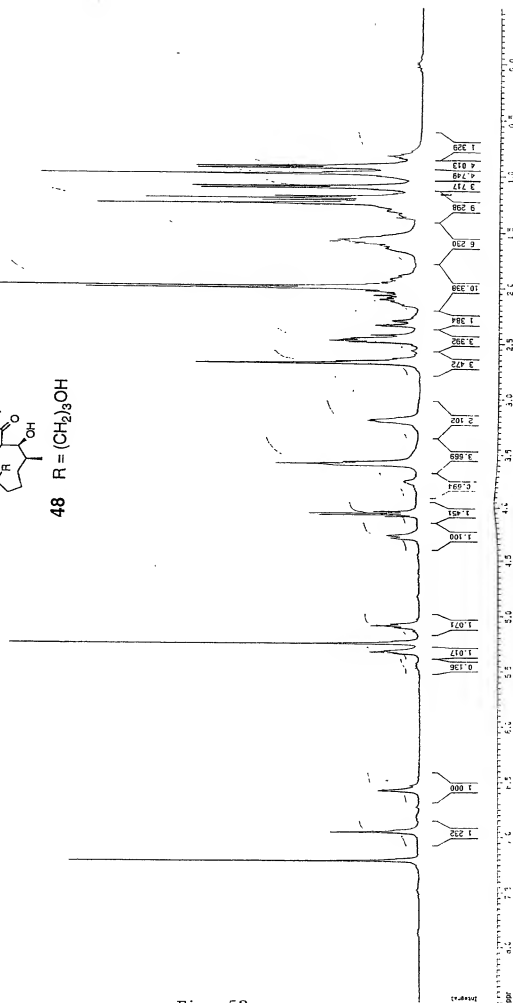


Fig. 52

FIG. 1A

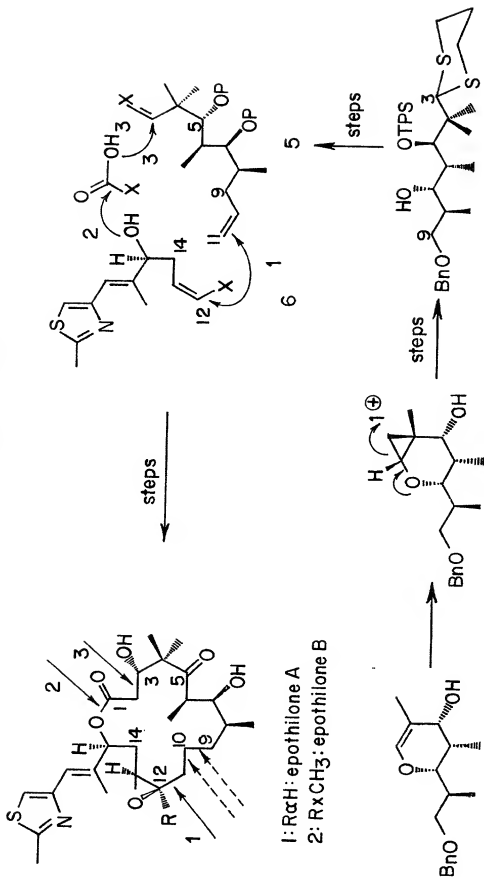


FIG. 12B

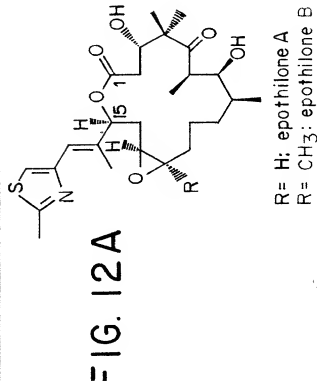
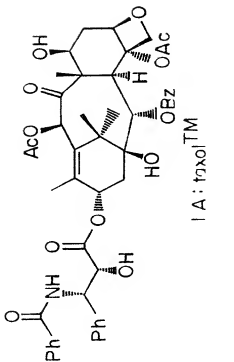
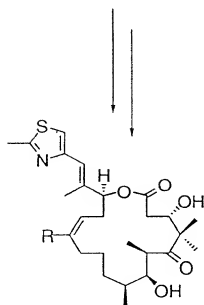
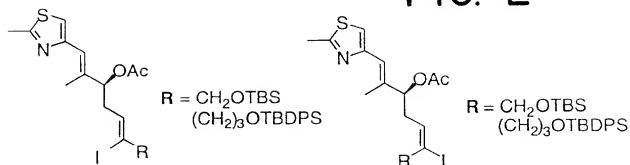


FIG. 12A



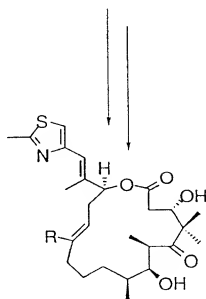
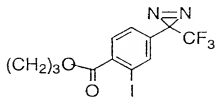
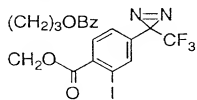
3/76

FIG. 2



$R = \text{CH}_2\text{OH}$

$(\text{CH}_2)_3\text{OH}$



$R = \text{CH}_2\text{OH}$
 $(\text{CH}_2)_2\text{OH}$

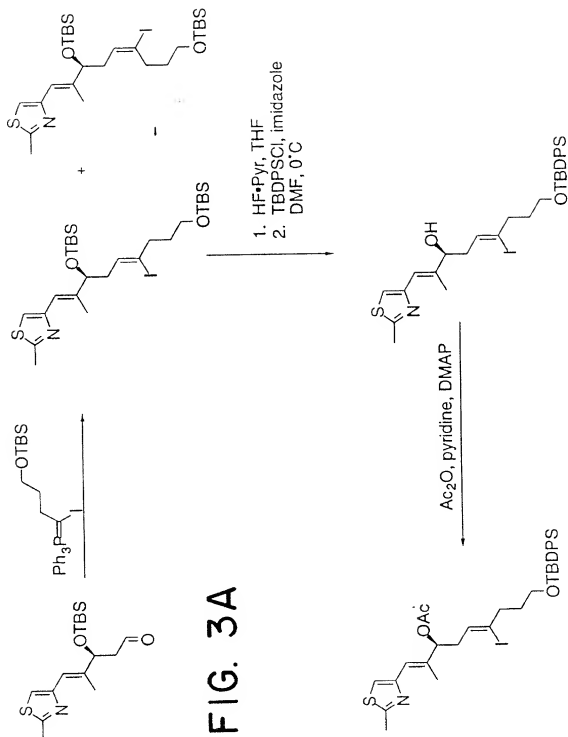


FIG. 3A

FIG. 3B

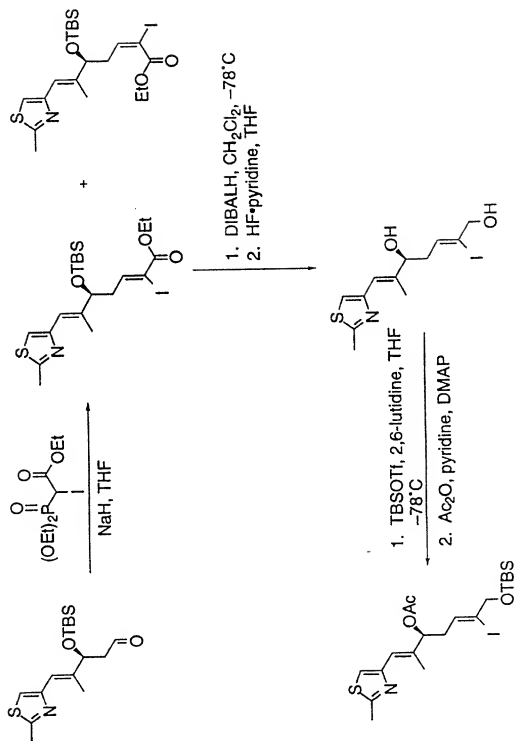
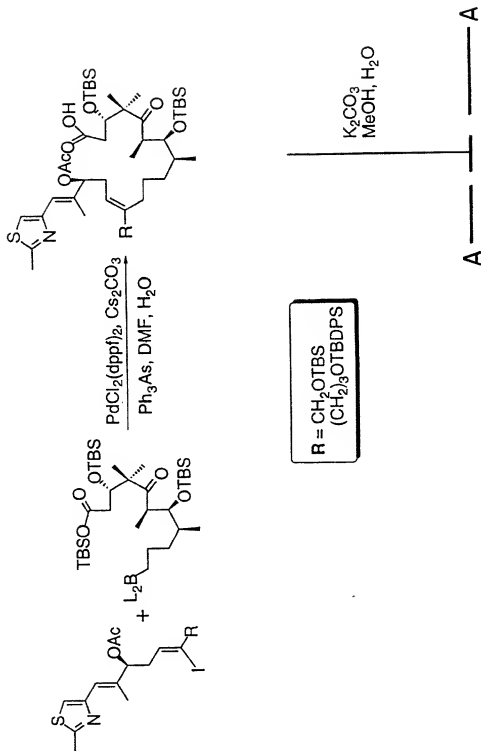


FIG. 3C



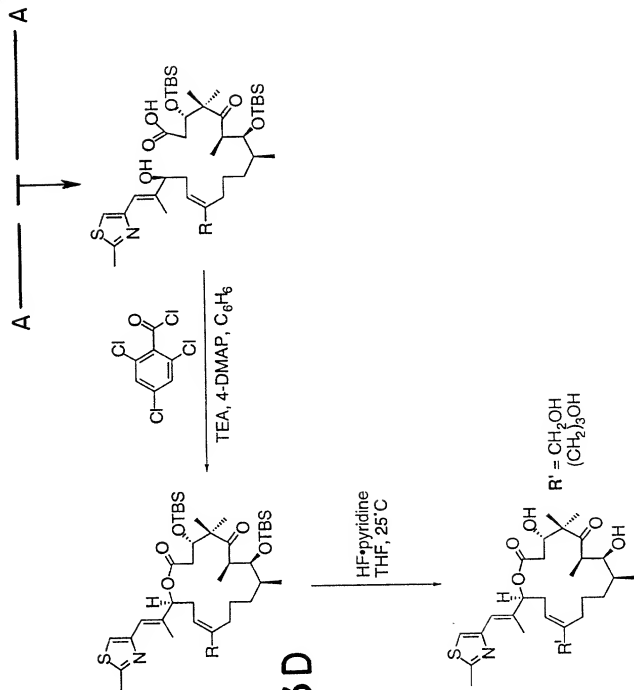


FIG. 3D

FIG. 3E

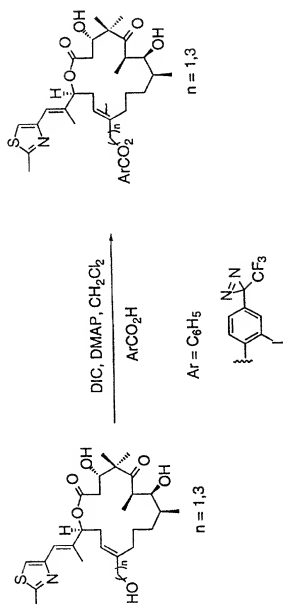


FIG. 3F

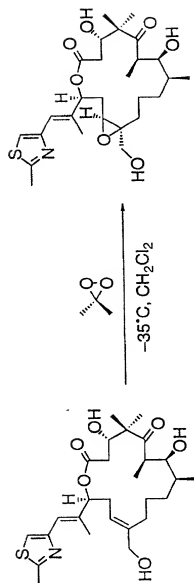


FIG. 4A

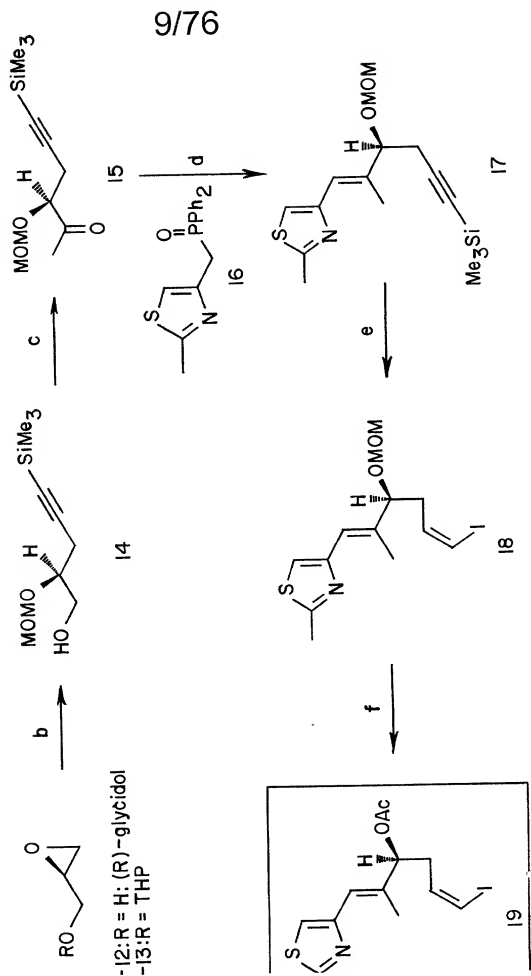


FIG. 4B

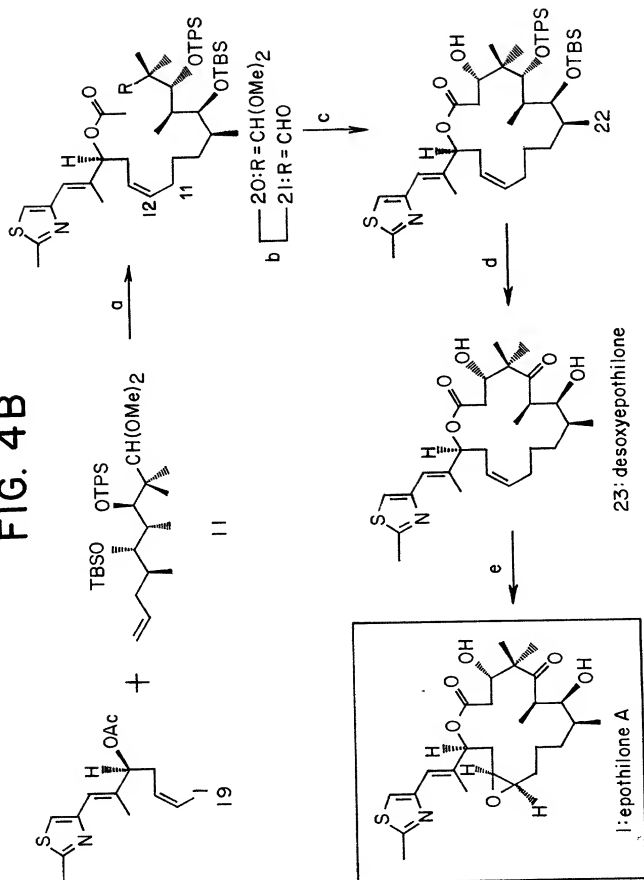
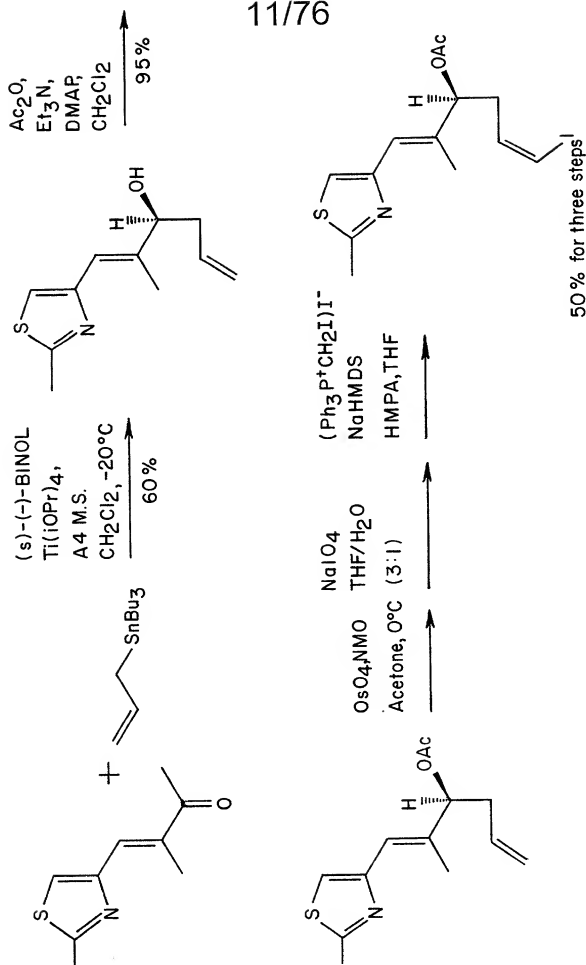


FIG. 5



11/76

FIG. 6A

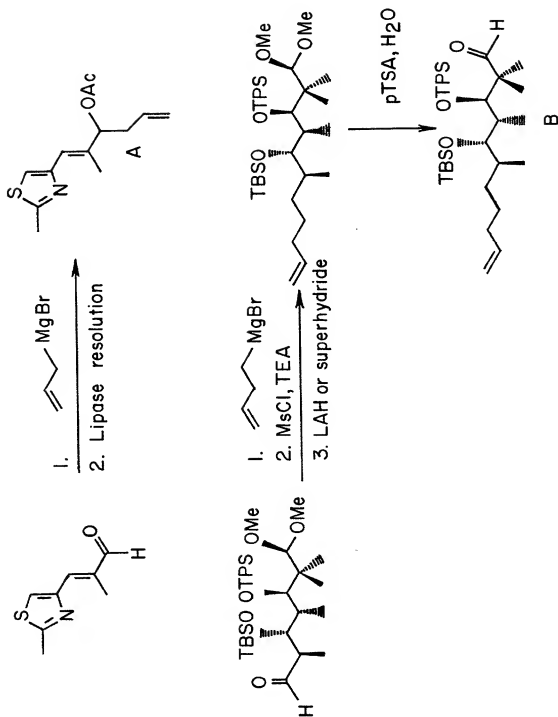
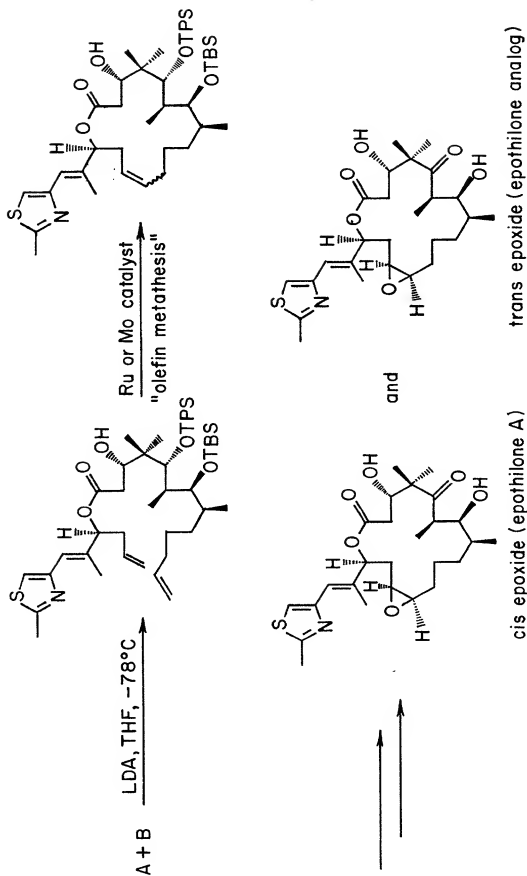


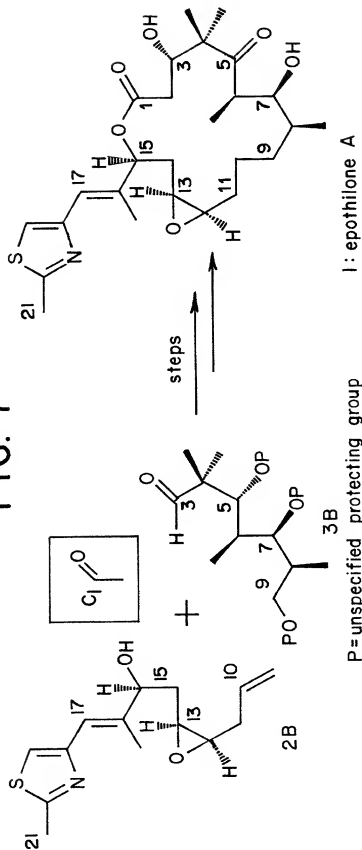
FIG. 6B



*17 steps from known starting materials vs. 27 steps for aldol macrocyclization

14/76

FIG. 7



Convergent strategy for a total synthesis of epothilone A (1).

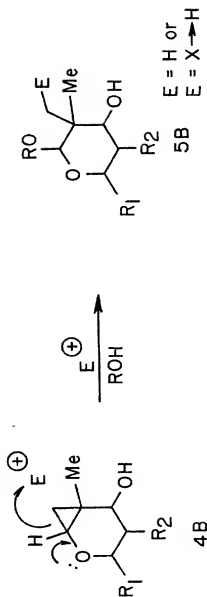
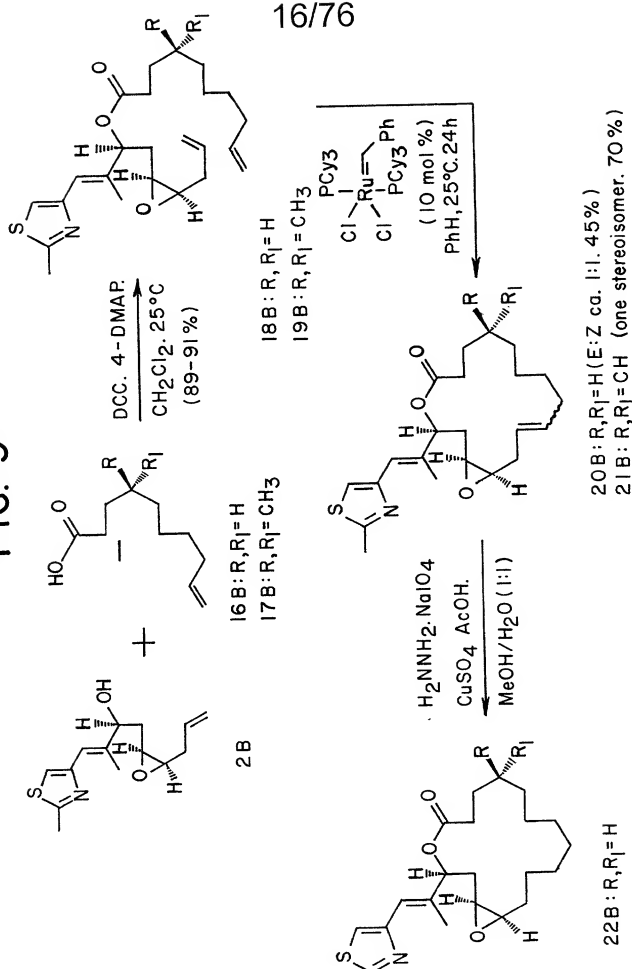
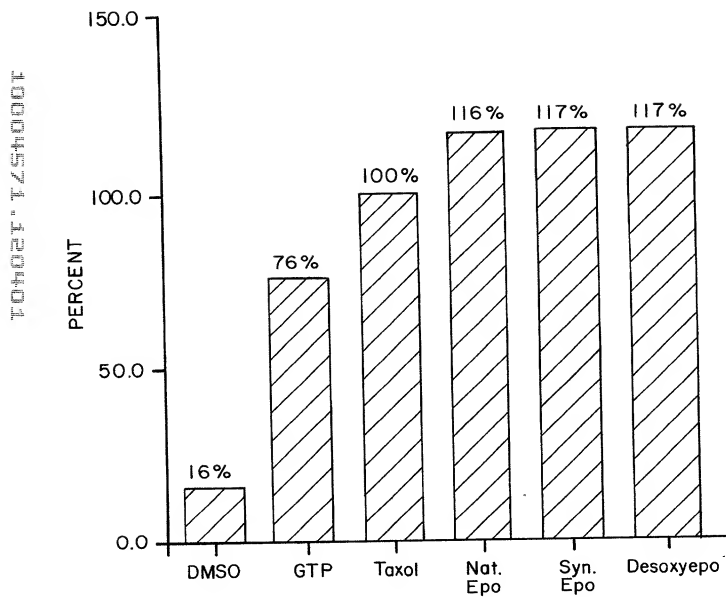


FIG. 9



17/76

FIG. 10



18/76

FIG. II

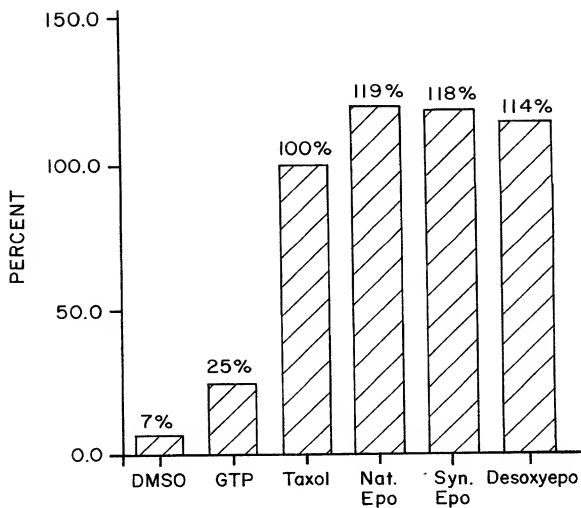


FIG. 13

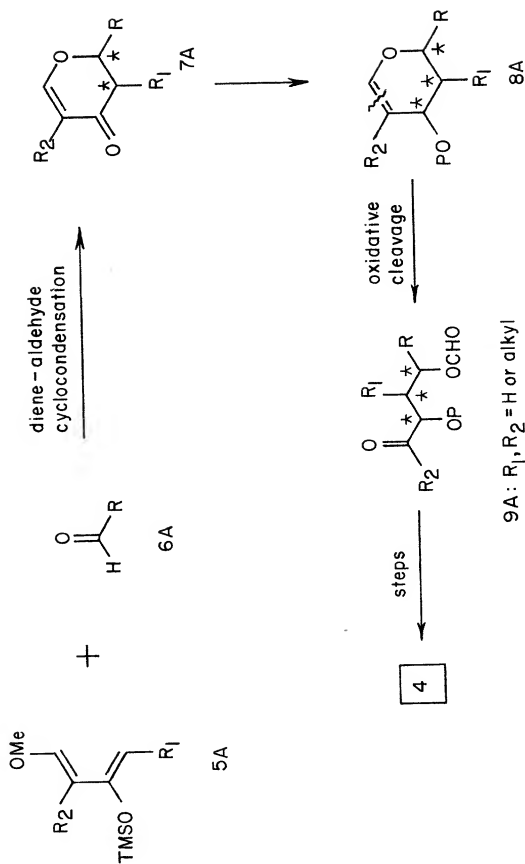
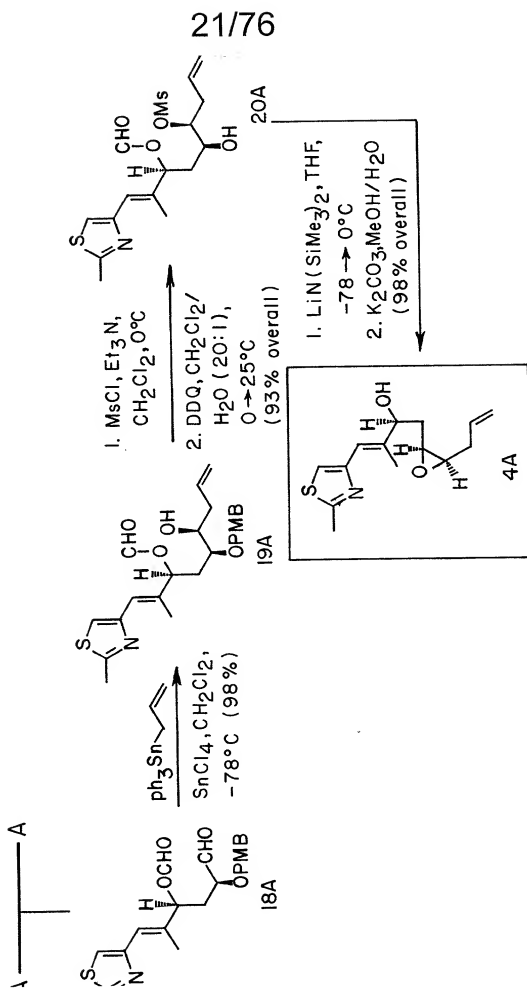


FIG. 14B



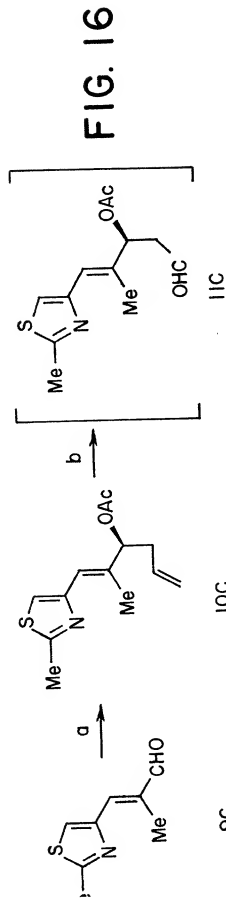


FIG. 16

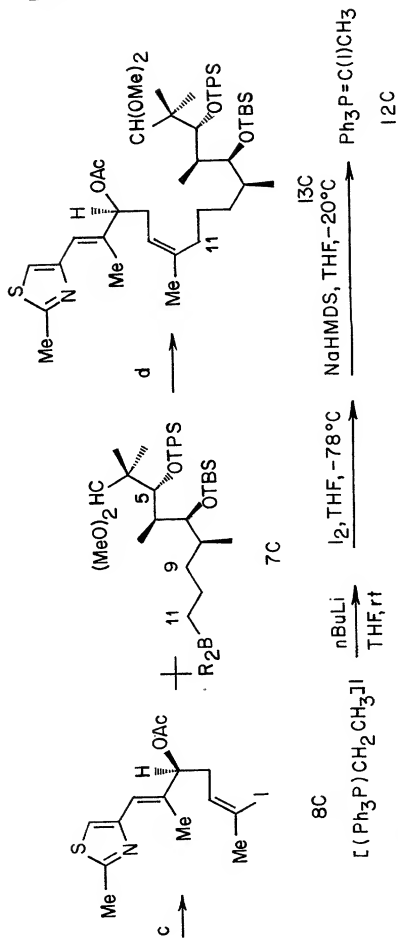
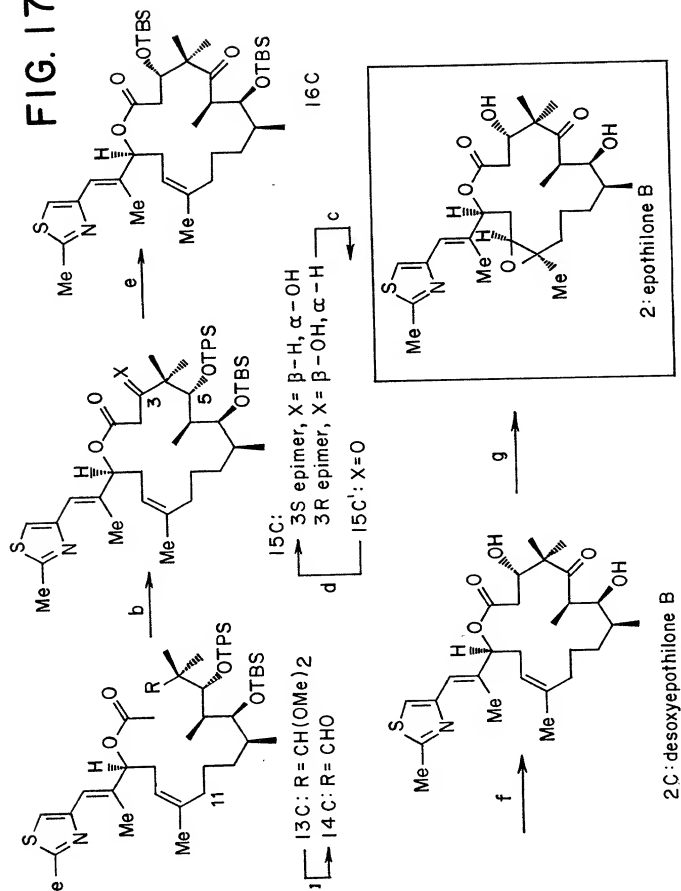


FIG. 17



25/76

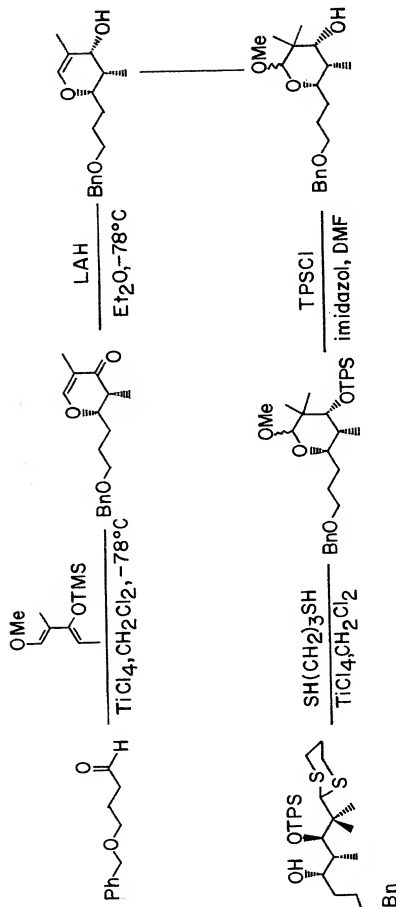


FIG. 18A

FIG. 18B



FIG. 19A

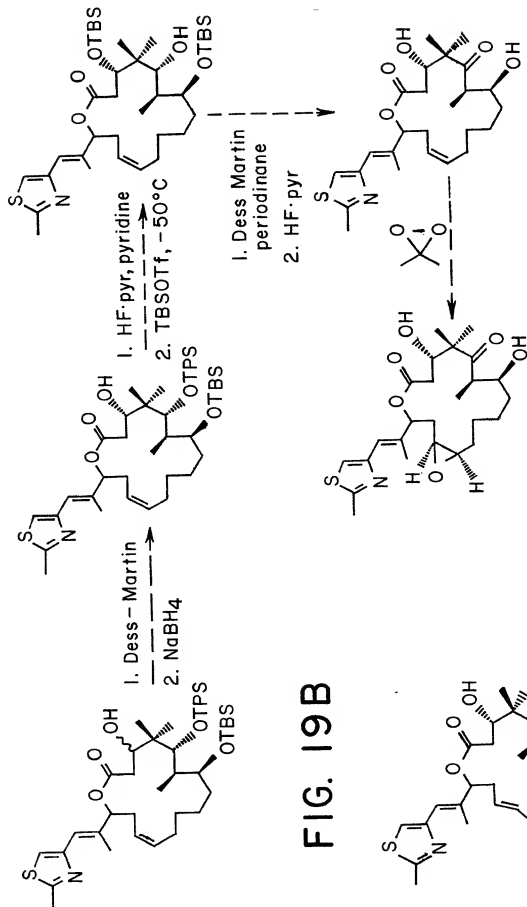
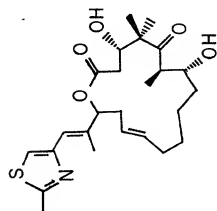


FIG. 19B



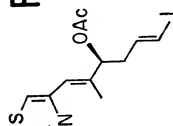


FIG. 19C

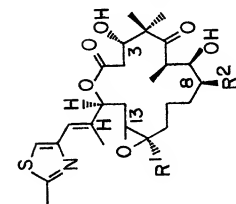
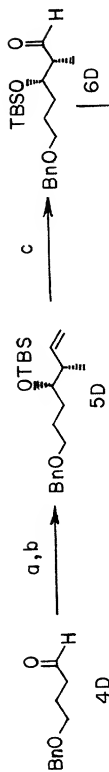


FIG. 20A

$R^1 = H, R^2 = Me$; epothilone A

$R^1 = R^2 = Me$; epothilone B

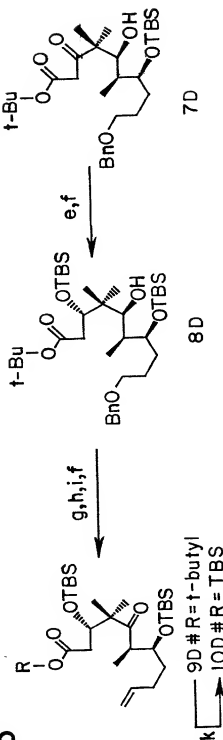
$R^1 = R^2 = H$; C₈-desmethyl-epothilone A (3D)



28/76

TBS = Sit-buMe₂

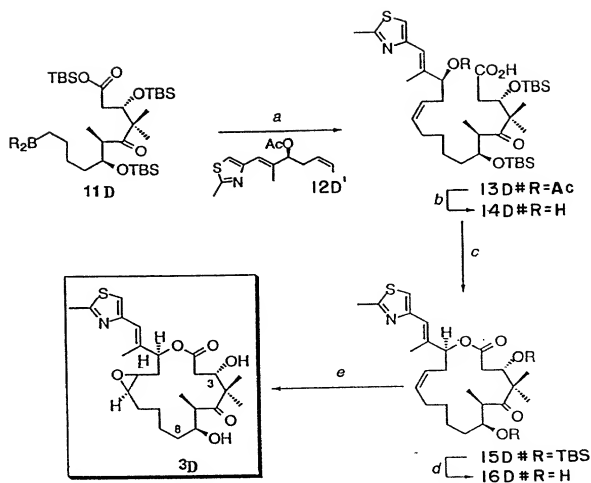
FIG. 20B



9D # R = t-butyl
10D # R = TBS

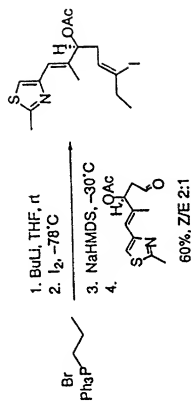
29/76

FIG. 21



10004571.1.20401

FIG. 22A



30/76

FIG. 22 B

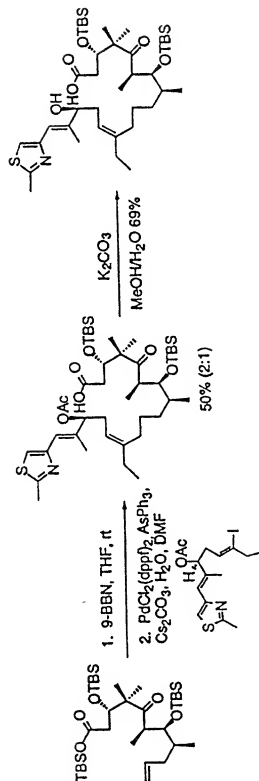


FIG. 22C

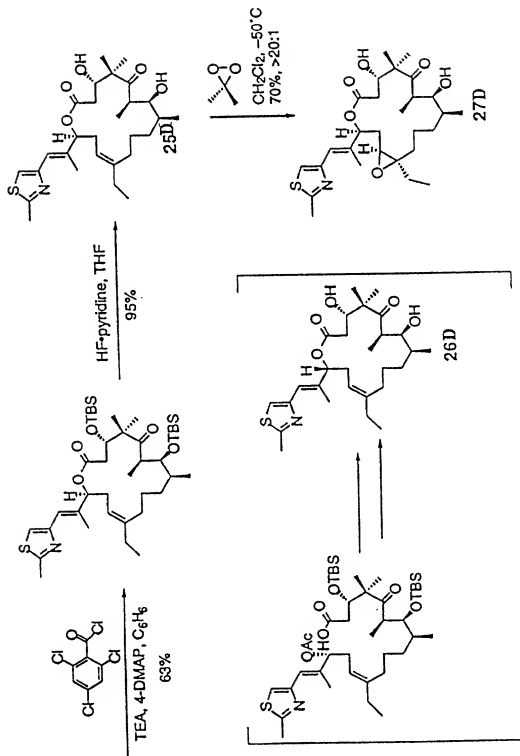


FIG. 23A

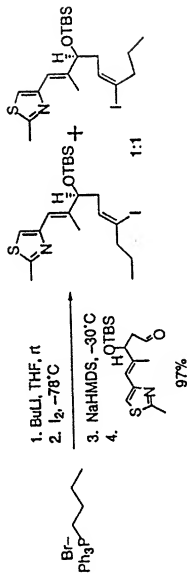


FIG. 23B

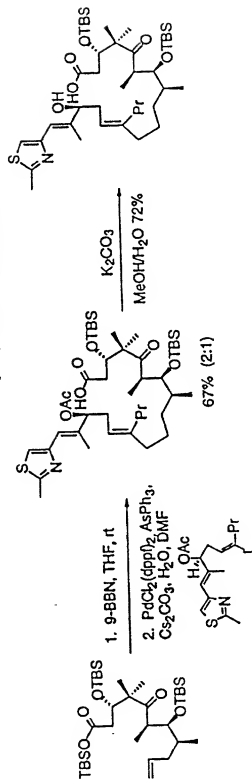


FIG. 23C

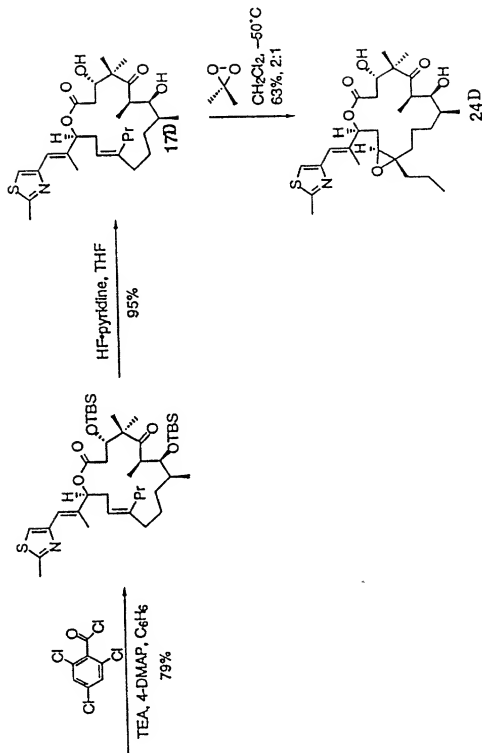
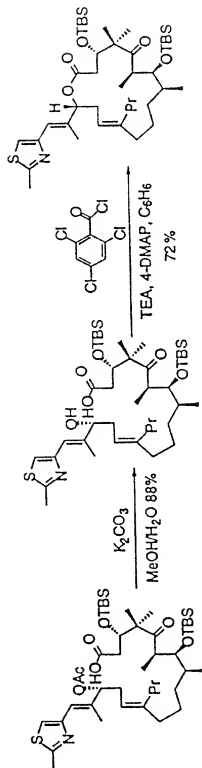


FIG. 24A



minor product from Suzuki
coupling reaction

FIG. 24B

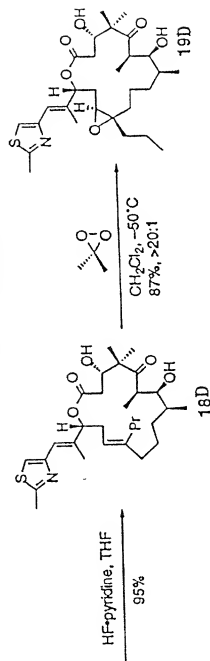


FIG. 25A

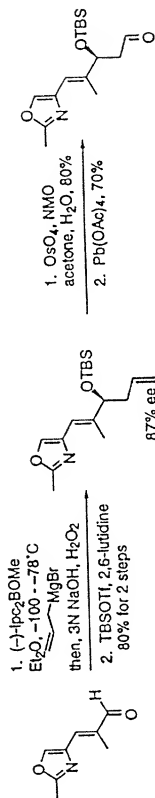


FIG. 25B

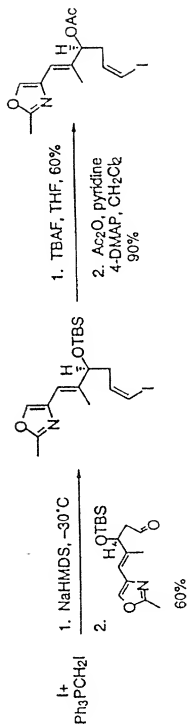


FIG. 25C

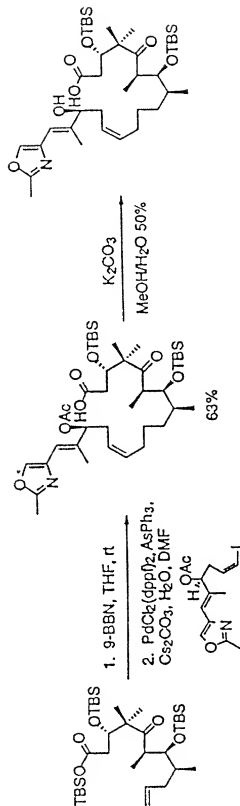


FIG. 25D

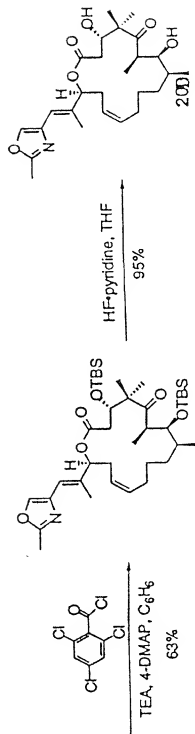


FIG. 26A

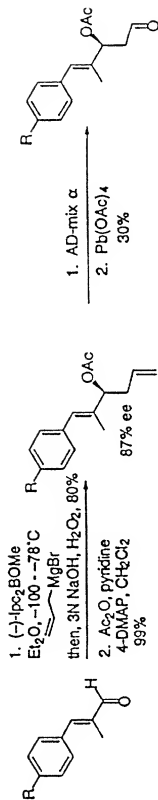
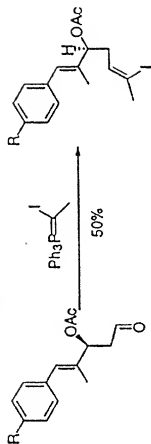


FIG. 26B



R = H, F, CF₃
 R=H is the only compound
 completed, F and CF₃ are nearly
 completed

FIG. 26C

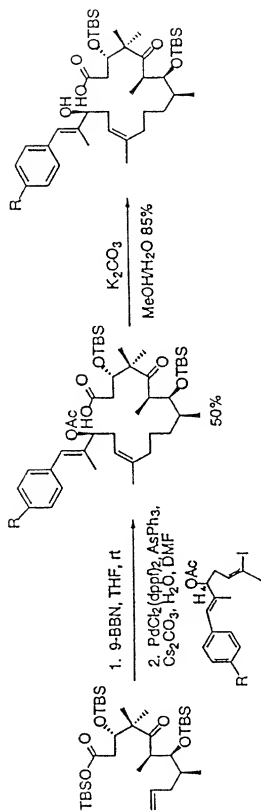


FIG. 26D

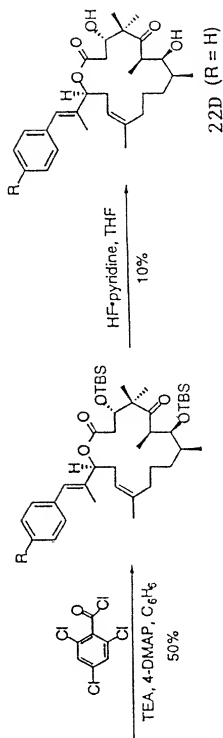


FIG. 27A

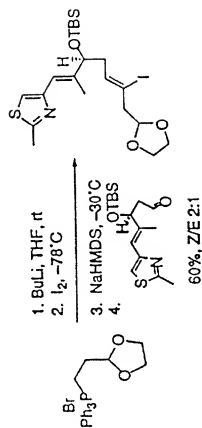


FIG. 27B

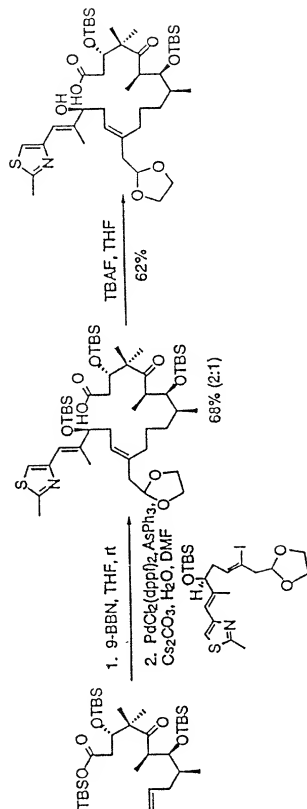
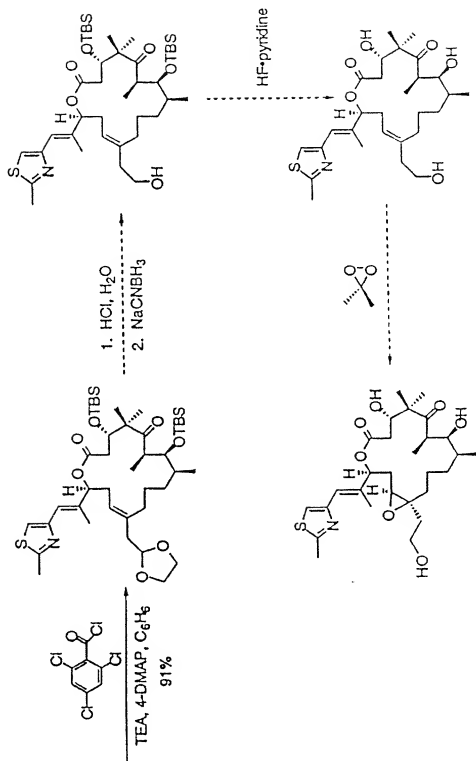
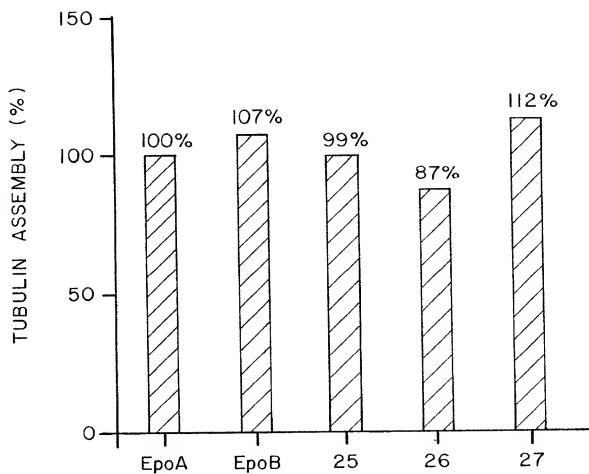


FIG. 27C



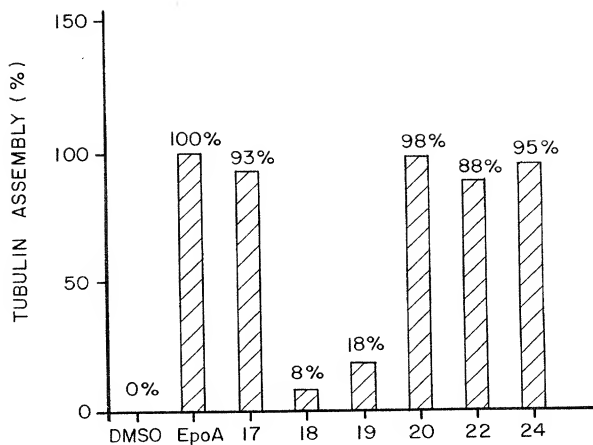
41/76

FIG. 28A



42/76

FIG. 28B



10004571-12500001

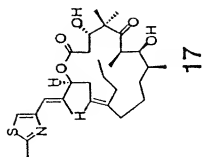
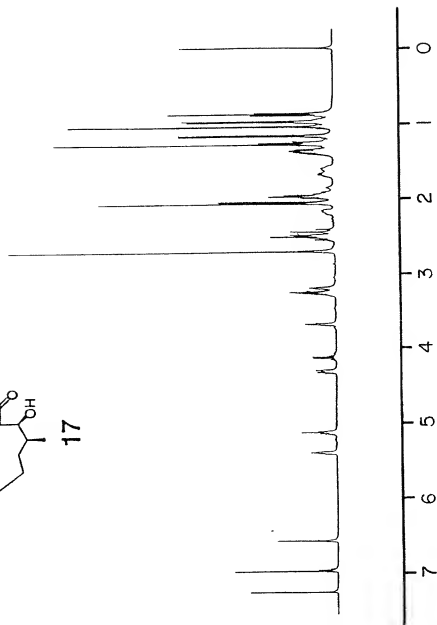


FIG. 29



T0402T-F254000T

FIG. 30

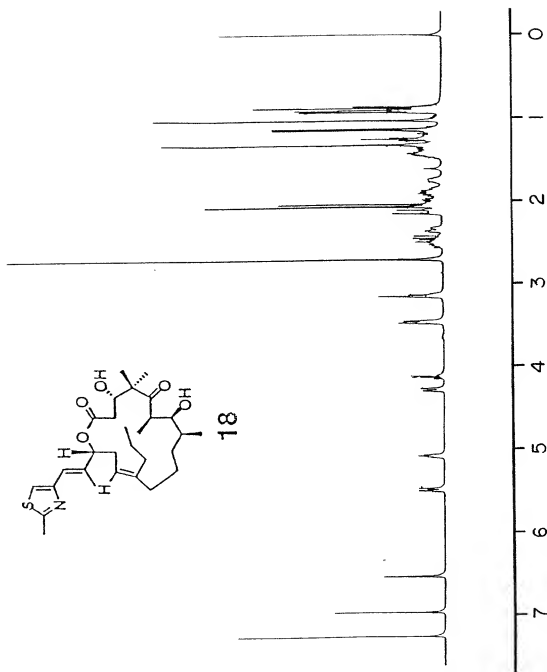
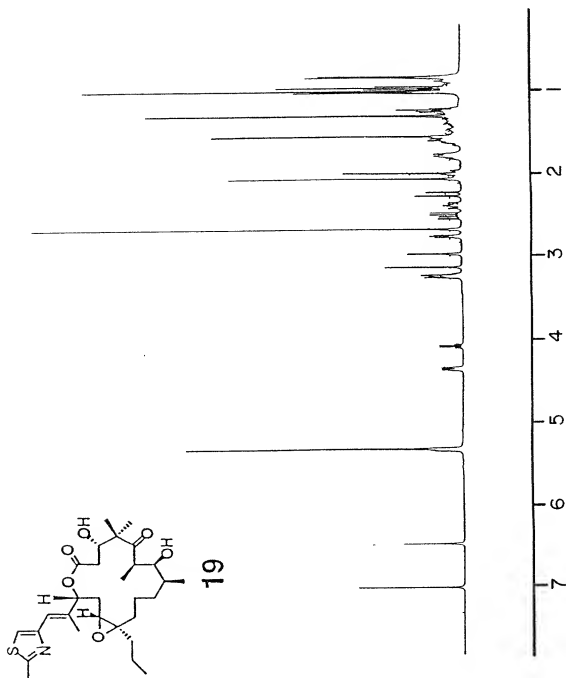
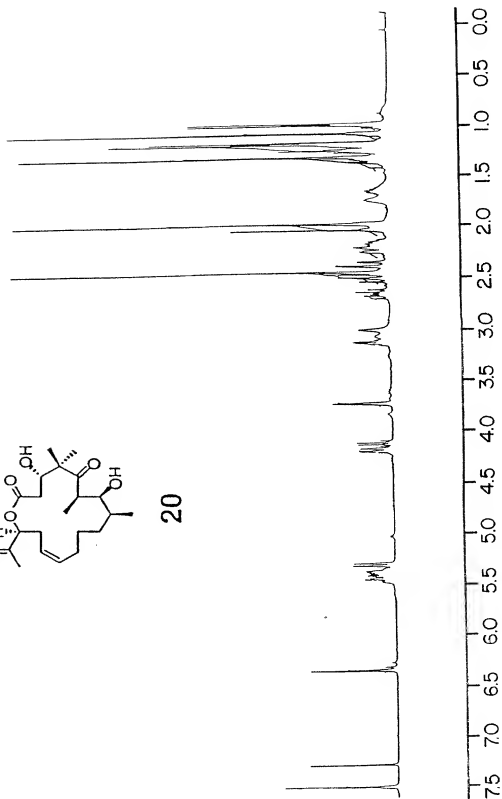
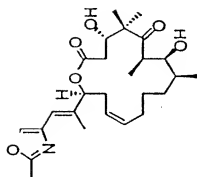


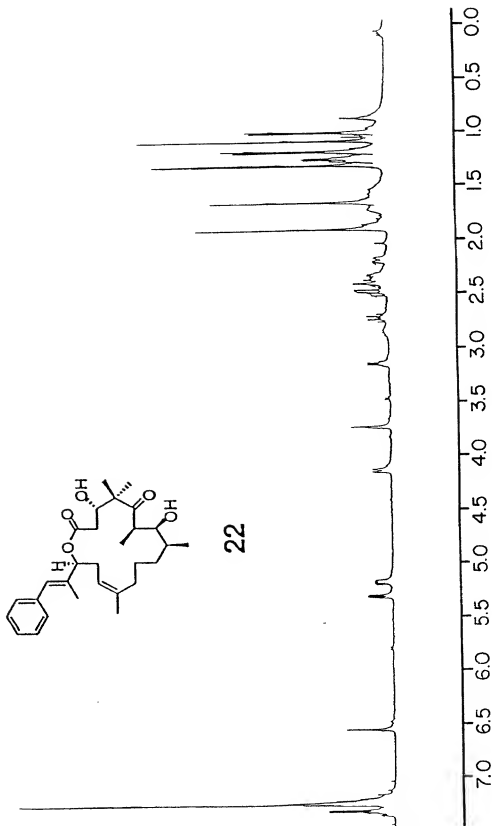
FIG. 31



20

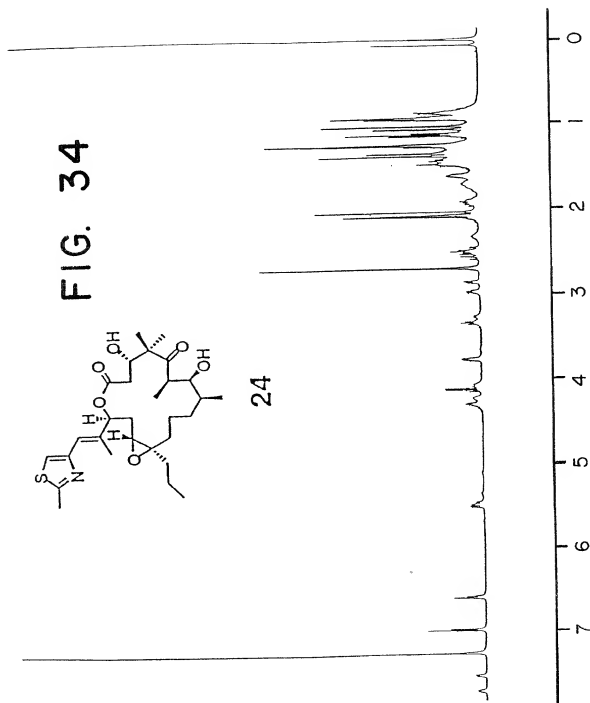


22



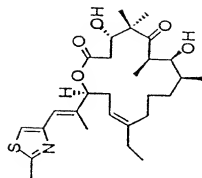
48/76

104021-1250001

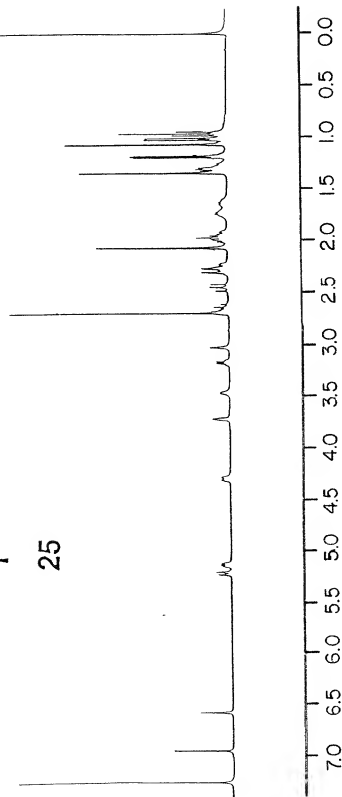


49/76

FIG. 35



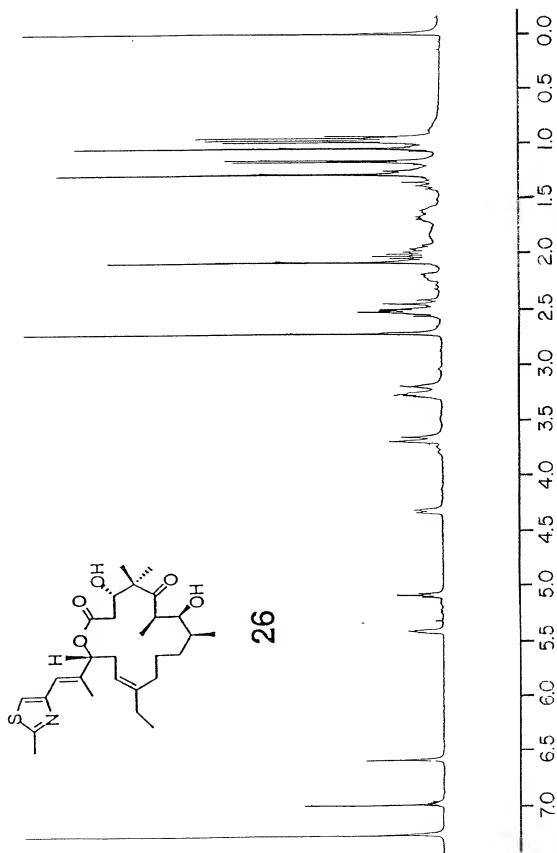
25



25

50/76

FIG. 36



51/76

FIG. 37

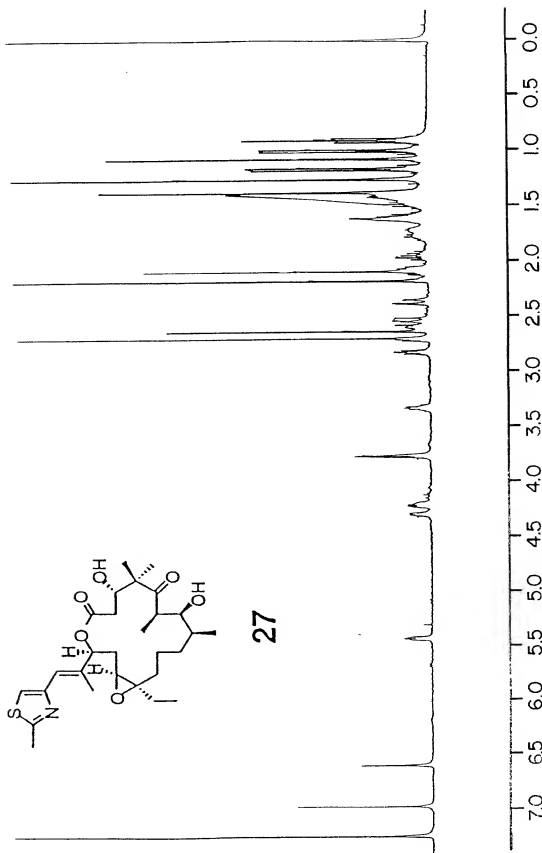
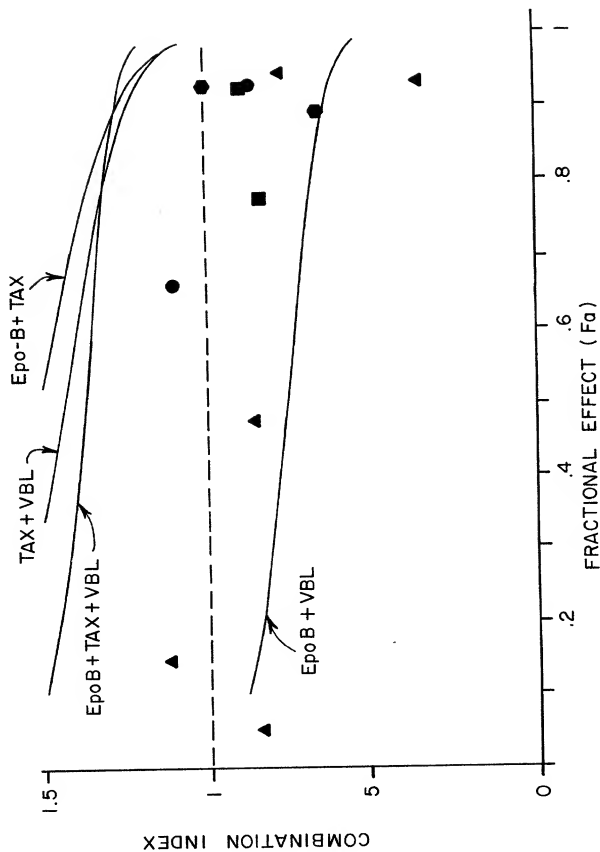
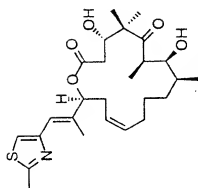


FIG. 38



53/76

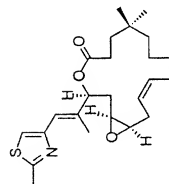
FIG. 39A



desoxyepothilone A

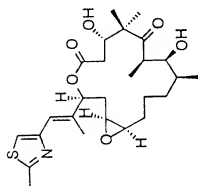
1

(0.022)
[0.012]



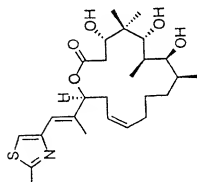
3

(271.1)
[22.4]



epothilone A

(0.0027)
[0.020]



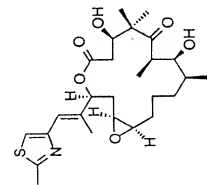
2

(14.23)
[6.28]

4

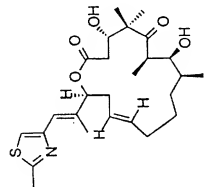
(2.12)
[43.0]

FIG. 39B



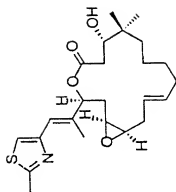
5

(>20)
[35.2]



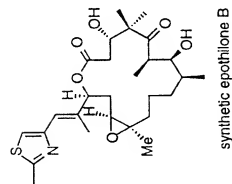
6

(0.052)
[0.035]

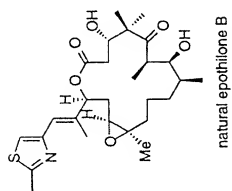


7

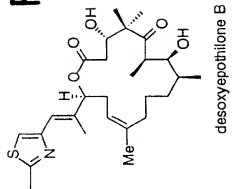
(7.36)
[9.82]



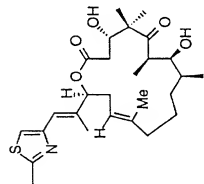
8
(0.00044)
[0.0026]



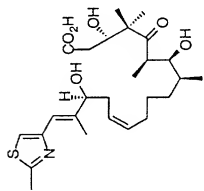
9
(0.00017)
[0.0012]



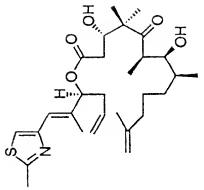
10
(0.0095)
[0.017]



11
(0.090)
[0.262]



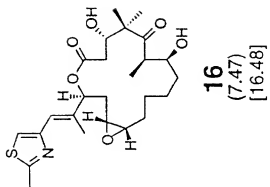
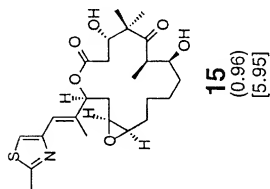
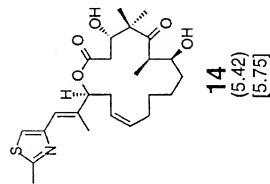
12
(0.79)
[>5]



13
(11.53)
[5.63]

FIG. 40A

FIG. 40B



57/76

FIG. 41A

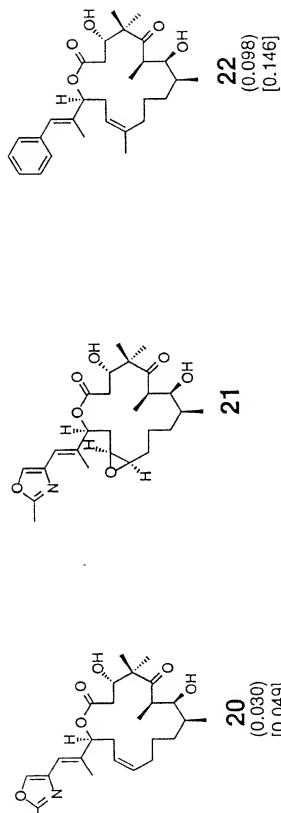
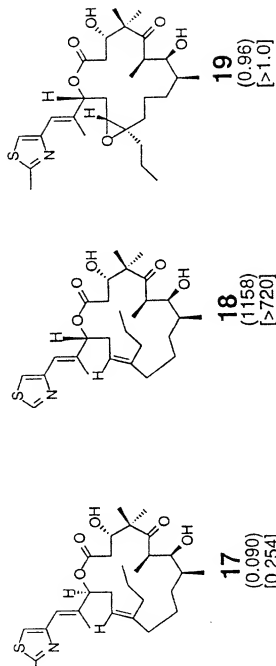
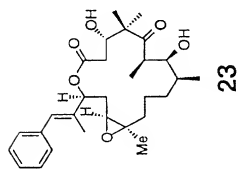
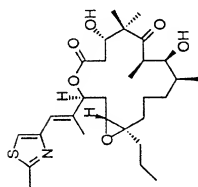


FIG. 41B

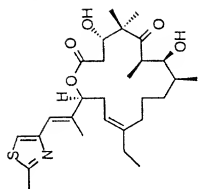


23



24

(0.0043)
f0.0321



25

(0.021)
f0.0771

FIG. 42A

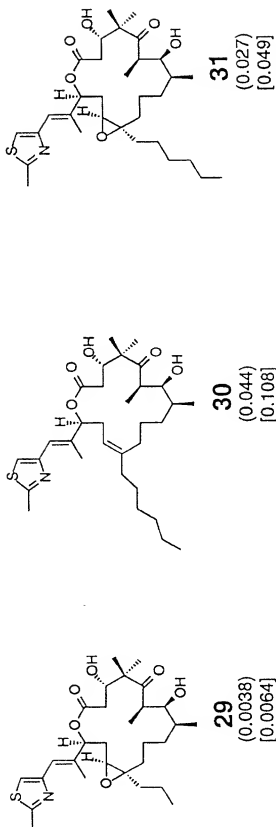
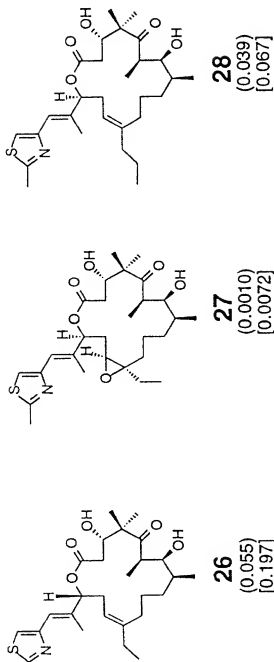


FIG. 42B

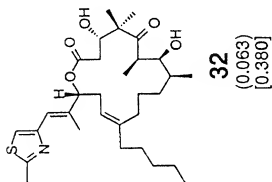
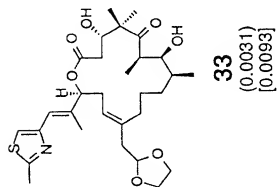
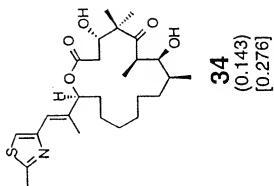


FIG. 42C

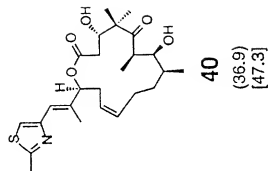
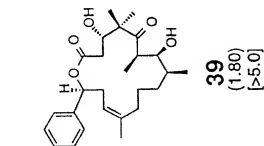
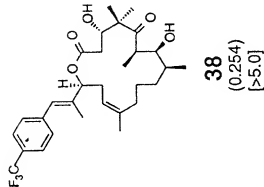
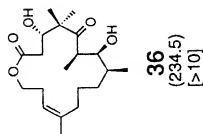
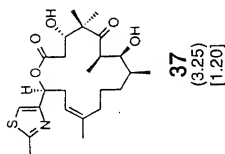
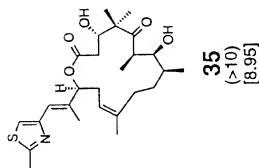


FIG. 42 D

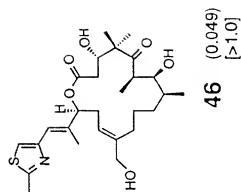
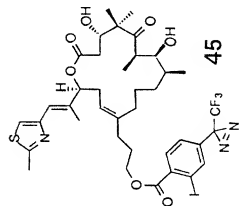
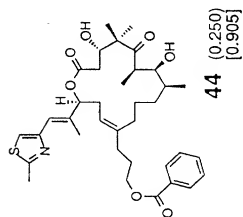
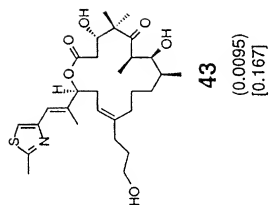
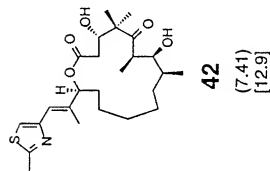
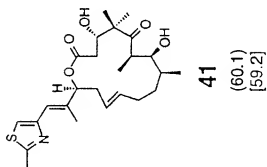
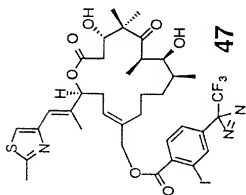
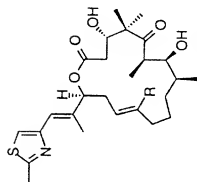


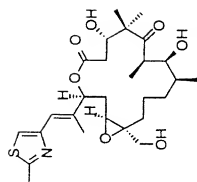
FIG. 42 E



47



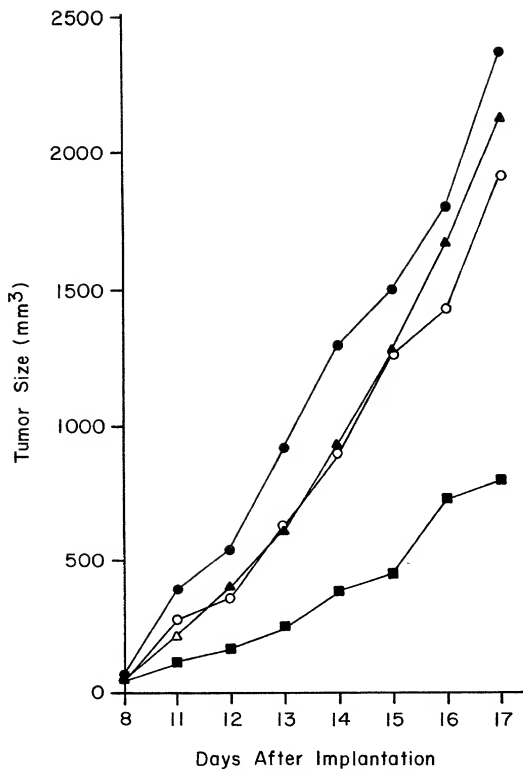
48 $\text{R} = (\text{CH}_2)_3\text{OH}$



49

64/76

FIG. 43A



65/76

FIG. 43B

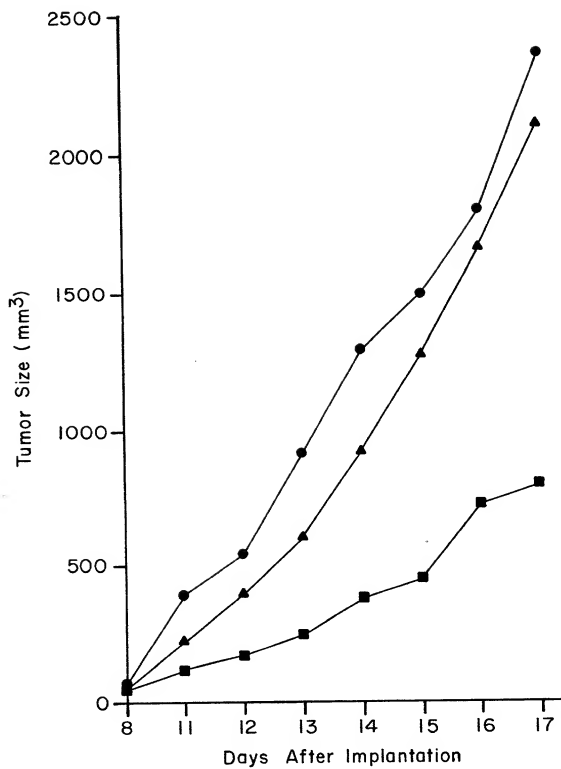
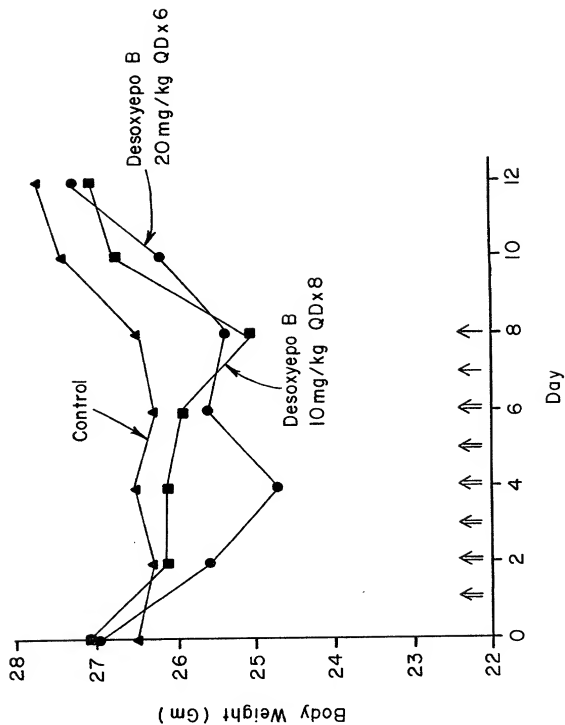
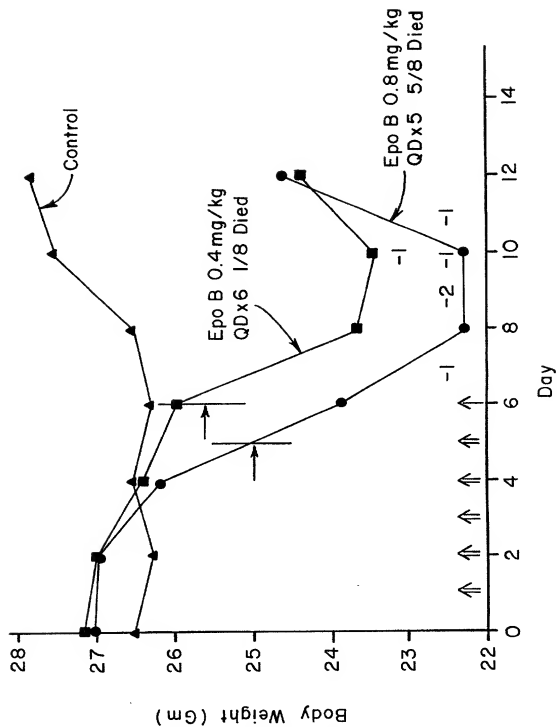


FIG. 44A



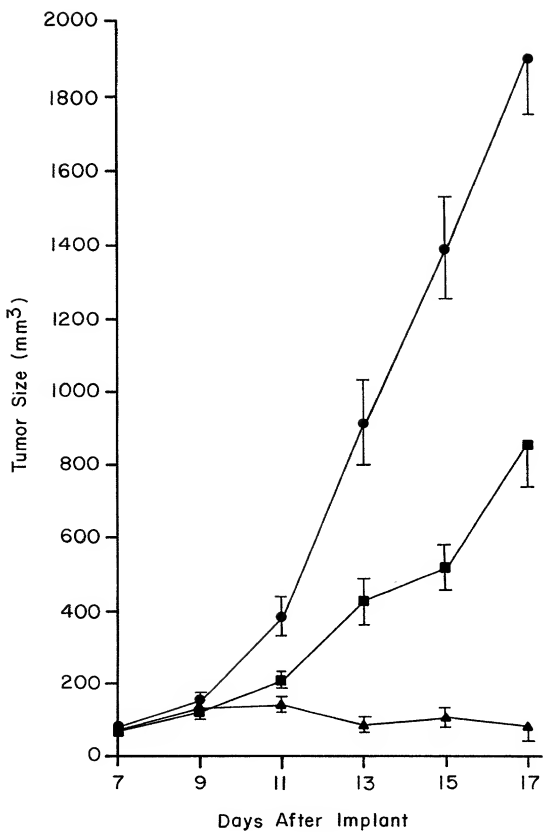
FOH02T 12540001

FIG. 44 B



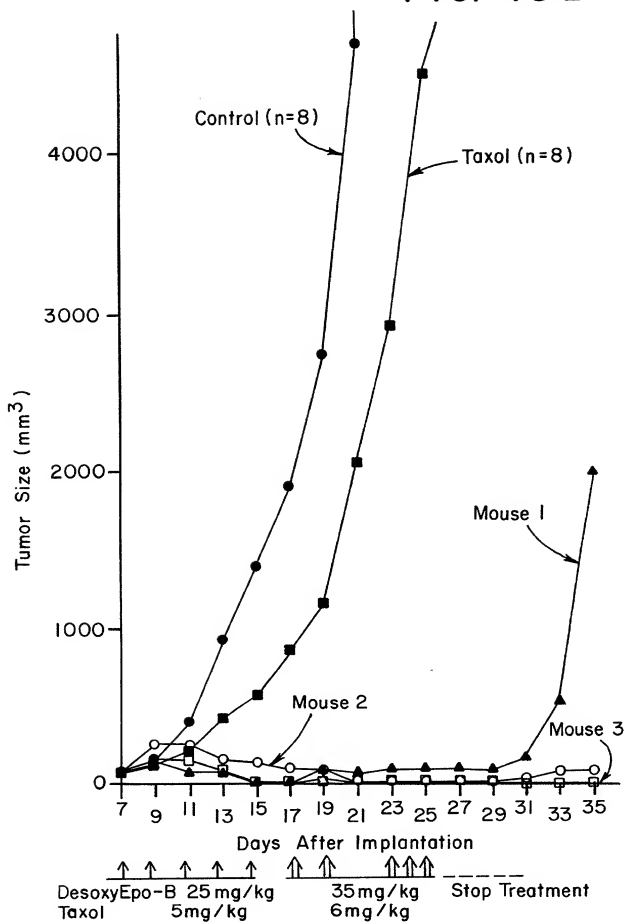
68/76

FIG. 45A



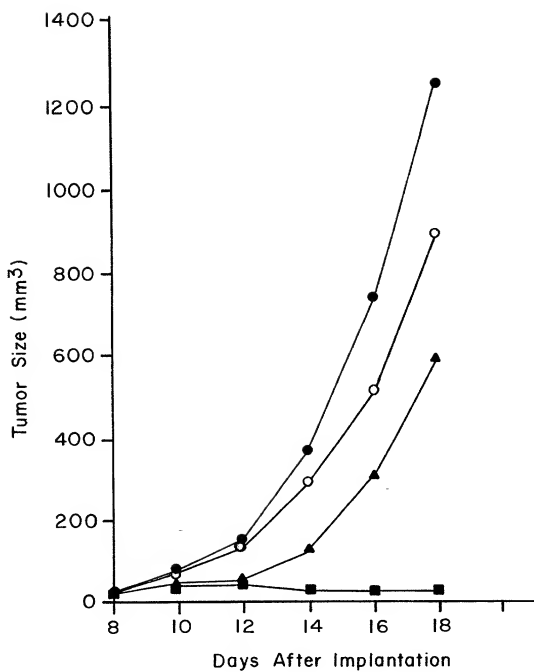
69/76

FIG. 45 B



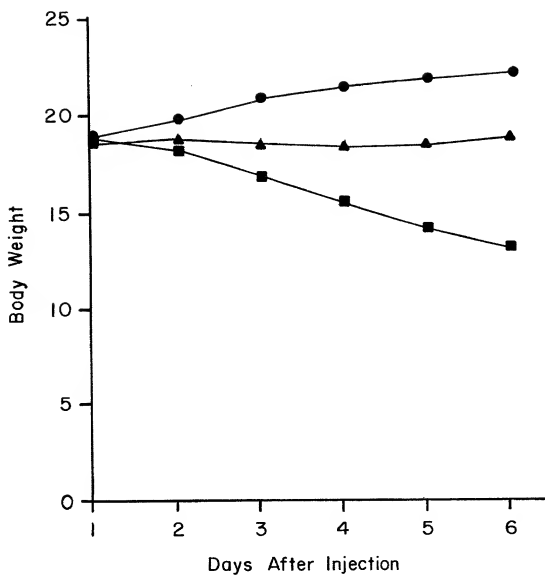
70/76

FIG. 46



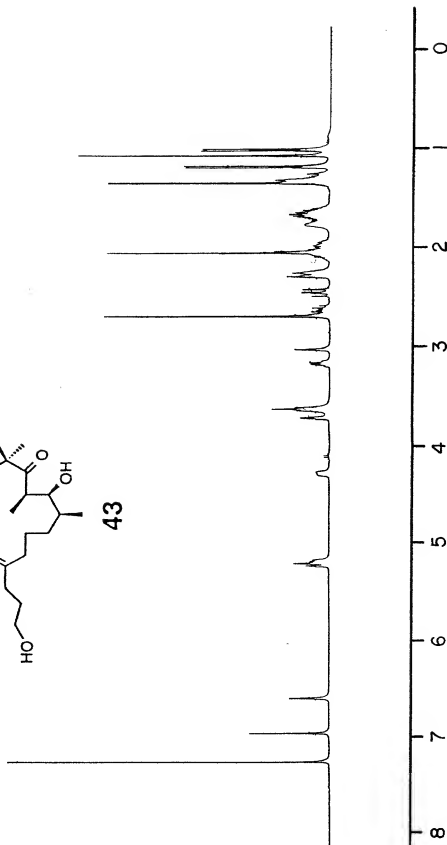
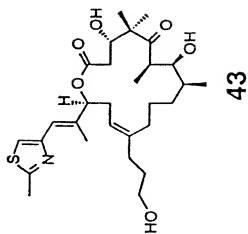
71/76

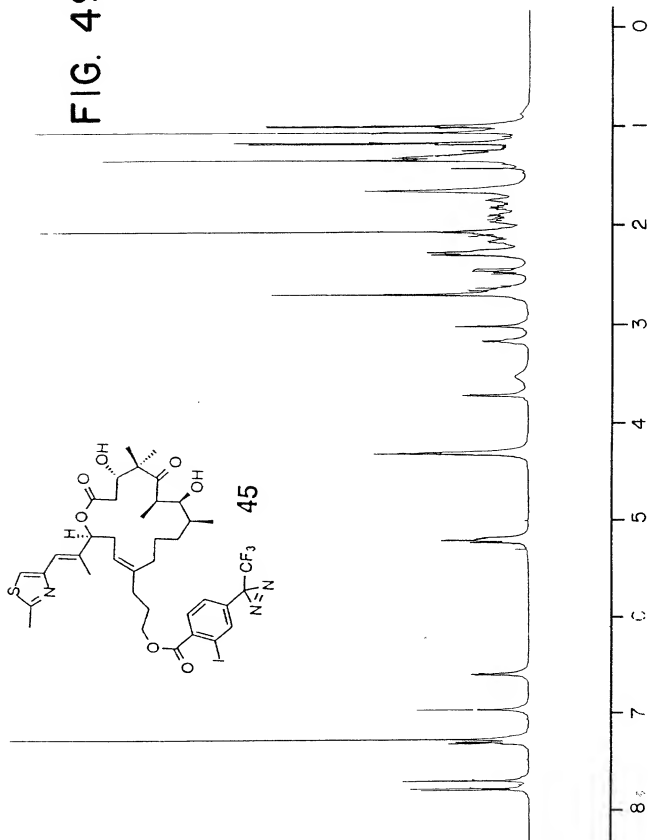
FIG. 47



100457-120401

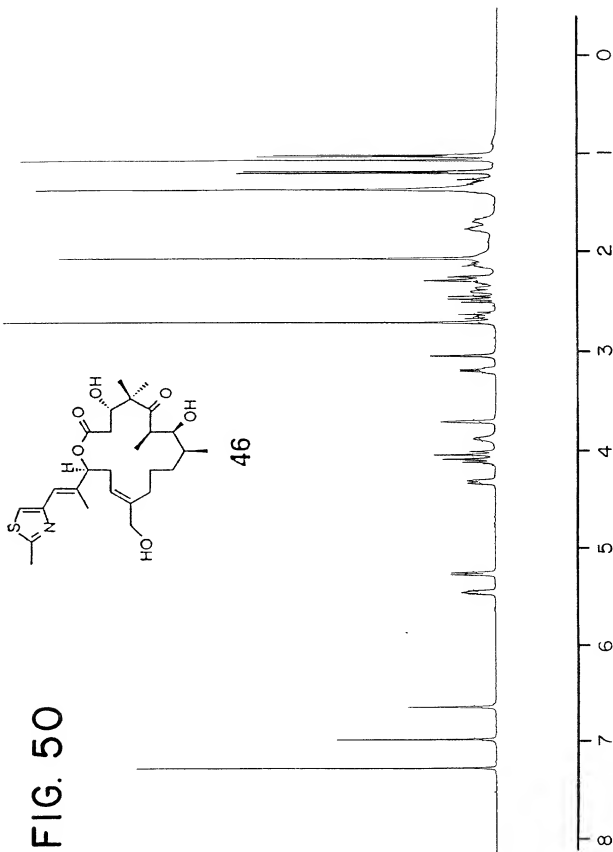
FIG. 48





74/76

104021-12540001



76/76

FIG. 52

